98590

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: P. Spiack Examiner #: 70400 Date: 7/3/03
Art Unit: 1614 Phone Number 30 84703 Serial Number: 10/079703
Mail Box and Bldg/Room Location: 2D03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Combo. of Angiotensin II antagonists & ACE inhibitor.

Inventors (please provide full names): Craig Anderson } Inventors / search
Salim Yusuf }

Earliest Priority Filing Date: 2/20/02

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search:

dementia senile amentia

RECEIVED
JUL 14 2003

Please show structures.

Thanks

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STAFF USE ONLY

Searcher: _____
Searcher Phone: _____
Searcher Location: _____
Date Searcher Picked Up: 7-14-03
Date Completed: 7-14-03
Searcher Prep & Review Time: 12
Clerical Prep Time: _____
Online Time: 51

Point of Contact:
Alexandra Waclawiw
Technical Info. Specialist
CM1 6A02 Tel: 308-4491

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic ✓
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN $1,103.00
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

33

51

PTO-1590 (8-01)

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=> d his

     (FILE 'HOME' ENTERED AT 11:09:07 ON 14 JUL 2003)

     FILE 'REGISTRY' ENTERED AT 11:09:15 ON 14 JUL 2003
                E ANGIOTENSIN II/CN
L1              1 S E3
                E ANGIOTENSIN CONVERTING ENZYME/CN
                E BENAZEPRIL/CN
                E BENAZEPRIL/CN
L2              2 S E3-4
                E CAPTOPRIL/CN
L3              1 S E3
                E CERONAPRIL/CN
L4              1 S E3
                E ENALAPRIL/CN
L5              1 S E3
                E FOSINOPRIL/CN
L6              1 S E3
                E IMIDAPRIL/CN
L7              1 S E3
L8              1 S E4
                E LISINOPIRL/CN
L9              1 S E4
                E MOEXIPRIL/CN
L10             1 S E3
L11             1 S E4
                E QUINAPRIL/CN
L12             2 S E3-4
                E RAMIPRIL/CN
L13             1 S E3
L14             1 S E5
                E TRANDOLAPRIL/CN
L15             2 S E4-5
                E PERINDOPRIL/CN
L16             2 S E4 OR E6
L17            19 S L2-L16
                E SARTAN/CN
                E SARATAN/CN
                E SARTAN/CN

     FILE 'HCAPLUS' ENTERED AT 11:13:58 ON 14 JUL 2003

     FILE 'REGISTRY' ENTERED AT 11:15:45 ON 14 JUL 2003

     FILE 'HCAPLUS' ENTERED AT 11:16:10 ON 14 JUL 2003
                E SARTAN/CT
L18         22665 S L1 OR ANGIOTENSIN II
L19          3346 S L18 (L) ANTAGONIS?
L20         10175 S ANGIOTENSIN CONVERT? ENZYME?

     FILE 'HCAPLUS' ENTERED AT 11:25:11 ON 14 JUL 2003

     FILE 'REGISTRY' ENTERED AT 11:25:32 ON 14 JUL 2003
L21             1 S 9015-82-1

     FILE 'HCAPLUS' ENTERED AT 11:25:38 ON 14 JUL 2003
L22          7583 S (L20 OR ACE) (L) INHIBIT?
L23         13350 S L22 OR L21
L24          7457 S L17
```

L25	17220	S	L23 OR L24
L26	679	S	L25 AND L19
L27	46585	S	DEMENTIA OR MENTAL (L) (DISORDER OR DISEASE) OR SENIL?
L28	9	S	L26 AND L27
L29	18	S	SARTAN OR SARTAN/AB
L30	1	S	L29 AND L25
L31	17	S	L29 NOT L30
		E	ANDERSON C/AU
L32	938	S	E3-60
		E	ANDERSON CRAIG/AU
L33	35	S	E3-11
		E	YUSUF S/AU
L34	393	S	E11 OR E3-9
		E	SLEIGHT P/AU
L35	60	S	E3-4
		E	HILBRICH L/AU
L36	2	S	E4
L37	1421	S	L32-L36
L38	4	S	L37 AND L25 AND L19

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=> fil reg
FILE 'REGISTRY' ENTERED AT 11:32:20 ON 14 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   11 JUL 2003  HIGHEST RN 546834-22-4
DICTIONARY FILE UPDATES:  11 JUL 2003  HIGHEST RN 546834-22-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d que l1;d l1
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ANGIOTENSIN II"/CN



L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   11128-99-7  REGISTRY
CN   Angiotensin II (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1-8-Angiotensin I
MF   Unspecified
CI   COM, MAN
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
       CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CIN, CSCHEM,
       DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS,
       NAPRALERT, NIOSHTIC, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
           17540 REFERENCES IN FILE CA (1957 TO DATE)
             212 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           17602 REFERENCES IN FILE CAPLUS (1957 TO DATE)
               3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> d que l17;d rn cn l17 1-19
L2             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (BENAZEPRIL/CN OR "BENAZEPRIL
                 HYDROCHLORIDE"/CN)
L3             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CAPTOPRIL/CN
L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CERONAPRIL/CN
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  ENALAPRIL/CN
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  FOSINOPRIL/CN
L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  IMIDAPRIL/CN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "IMIDAPRIL HYDROCHLORIDE"/CN
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L9            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  LISINOPRIL/CN
L10           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  MOEXIPRIL/CN
L11           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "MOEXIPRIL HYDROCHLORIDE"/CN

L12           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (QUINAPRIL/CN OR "QUINAPRIL
                  HYDROCHLORIDE"/CN)
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  RAMIPRIL/CN
L14           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RAMIPRIL HYDROCHLORIDE"/CN
L15           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("TRANDOLAPRIL HYDROCHLORIDE"
                  /CN OR TRANDOLAPRILAT/CN)
L16           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PERINDOPRIL EBUMINE"/CN OR
                  "PERINDOPRIL HYDROCHLORIDE"/CN
L17          19 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L2 OR L3 OR L4 OR L5 OR L6
                  OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR
                  L16)
```

→ see printout at end. Originally forgot to print out structures

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L17  ANSWER 1 OF 19  REGISTRY  COPYRIGHT 2003 ACS
RN   217460-19-0  REGISTRY
CN   1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-
     (ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, monohydrochloride,
     (2S,3aS,7aS)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Perindopril hydrochloride

L17  ANSWER 2 OF 19  REGISTRY  COPYRIGHT 2003 ACS
RN   111223-26-8  REGISTRY
CN   L-Proline, 1-[(2S)-6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-
     oxohexyl]- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   L-Proline, 1-[6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-
     oxohexyl]-, (S)-
OTHER NAMES:
CN   Ceranapril
CN   Ceronapril
CN   SQ 29852

L17  ANSWER 3 OF 19  REGISTRY  COPYRIGHT 2003 ACS
RN   107133-36-8  REGISTRY
CN   1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-
     (ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,7aS)-, compd.
     with 2-methyl-2-propanamine (1:1) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)butyl]amino]-1-
     oxopropyl]octahydro-, [2S-[1[R*(R*)],2.alpha.,3a.beta.,7a.beta.]]-, compd.
     with 2-methyl-2-propanamine (1:1)
CN   2-Propanamine, 2-methyl-, (2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-
     (ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylate
     (9CI)
CN   2-Propanamine, 2-methyl-, [2S-[1[R*(R*)],2.alpha.,3a.beta.,7a.beta.]]-1-[2-
     [[1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-
     carboxylate
OTHER NAMES:
CN   Aceon
CN   Butylaminiperindopril
CN   Coversum
CN   Coversyl
```

CN McN-A 2833-109
CN **Perindopril ebumine**
CN Perindopril erbumine
CN Perindopril-tert-butylamine
CN Perinodpril erbimune
CN Prestarium
CN Procaptan
CN S 9490-3

L17 ANSWER 4 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 104196-00-1 REGISTRY
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, (2S,3aS,6aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, [2S-[1[R*(R*)],2.alpha.,3a.beta.,6a.beta.]]-
OTHER NAMES:
CN **Ramipril hydrochloride**

L17 ANSWER 5 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 103775-10-6 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, (3S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN **Moexipril**
CN RS 10085

L17 ANSWER 6 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 98048-97-6 REGISTRY
CN L-Proline, 4-cyclohexyl-1-[[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, [1[S*(R*)],2.alpha.,4.beta.]-
OTHER NAMES:
CN Fosenopril
CN **Fosinopril**

L17 ANSWER 7 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 89396-94-1 REGISTRY
CN 4-Imidazolidinecarboxylic acid, 3-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, monohydrochloride, (4S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4-Imidazolidinecarboxylic acid, 3-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, monohydrochloride, [4S-[3[R*(R*)],4R*]]-
OTHER NAMES:
CN **Imidapril hydrochloride**
CN Novaloc
CN TA 6366
CN Tanapril

L17 ANSWER 8 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 89371-37-9 REGISTRY
CN 4-Imidazolidinecarboxylic acid, 3-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4-Imidazolidinecarboxylic acid, 3-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, [4S-[3[R*(R*)],4R*]]-
OTHER NAMES:
CN **Imidapril**

L17 ANSWER 9 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 87725-72-2 REGISTRY
CN 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, (2S,3aR,7aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, [2S-[1[R*(R*)],2.alpha.,3a.alpha.,7a.beta.]]-
OTHER NAMES:
CN **Trandolapril hydrochloride**

L17 ANSWER 10 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 87679-71-8 REGISTRY
CN 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aR,7aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Indole-2-carboxylic acid, 1-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2.alpha.,3a.alpha.,7a.beta.]]-
OTHER NAMES:
CN RU 44403
CN **Trandolaprilat**
CN Trandolaprilate

L17 ANSWER 11 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 87333-19-5 REGISTRY
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,6aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2.alpha.,3a.beta.,6a.beta.]]-
OTHER NAMES:
CN Altace
CN Cardace
CN Delix
CN HOE 498
CN Pramace
CN Quark
CN Ramace
CN **Ramipril**
CN Triatec
CN Tritace
CN Unipril
CN Vesdil

L17 ANSWER 12 OF 19 REGISTRY COPYRIGHT 2003 ACS

RN 86541-75-5 REGISTRY
CN 1H-1-Benzazepine-1-acetic acid, 3-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, [S-(R*,R*)]-
OTHER NAMES:
CN Benapril
CN **Benazepril**
CN Briem
CN Cibacen
CN Cibacen WS
CN Cibacene

L17 ANSWER 13 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 86541-74-4 REGISTRY
CN 1H-1-Benzazepine-1-acetic acid, 3-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, (3S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, [S-(R*,R*)]-
OTHER NAMES:
CN **Benazepril hydrochloride**
CN CGS 14824A
CN CGS 14824A HCl
CN Lotensin
CN Lotension

L17 ANSWER 14 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 85441-61-8 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN Ectren
CN Koretic
CN **Quinapril**

L17 ANSWER 15 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 82586-55-8 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN Accupril
CN Accuprin
CN Accupro
CN Accupron
CN Acequide
CN Acequin

CN Acuitel
CN Acuprel
CN Acupril
CN Asig
CN CI 906
CN Korec
CN Korectic
CN PD 109452-2
CN **Quinapril hydrochloride**
CN Quinazil

L17 ANSWER 16 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 82586-52-5 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN CI 925
CN **Moexipril hydrochloride**
CN RS 10085-197
CN SPM 925
CN Univasc

L17 ANSWER 17 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 76547-98-3 REGISTRY
CN L-Proline, N2-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-, (S)-
OTHER NAMES:
CN Acerbon
CN Alapril
CN Carace
CN Cipral
CN Cipril
CN Coric
CN Inopril
CN Linopril
CN Linvas
CN Lipril
CN **Lisinopril**
CN Lisipril
CN Lisoril
CN Lispril
CN Listril
CN MK 521
CN MK 522
CN N-(1(S)-Carboxy-3-phenylpropyl)-L-lysyl-L-proline
CN N2-[(S)-1-Carboxy-3-phenylpropyl]-L-lysyl-L-proline
CN Noperten
CN Novatec
CN Presiten
CN Prinil
CN Prinivil
CN Prinvil
CN Tensopril

CN Tensyn
CN Vivatec
CN Zestril

L17 ANSWER 18 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 75847-73-3 REGISTRY
CN L-Proline, N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-
OTHER NAMES:
CN **Enalapril**

L17 ANSWER 19 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 62571-86-2 REGISTRY
CN L-Proline, 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-, (S)-
OTHER NAMES:
CN (-)-Captopril
CN Acediur
CN Aceplus
CN Acepress
CN Acepril
CN Alopresin
CN Capoten
CN Captolane
CN **Captopril**
CN Captoril
CN Cesplon
CN Dilabar
CN Garranil
CN Hipertil
CN L-Captopril
CN Lopirin
CN Lopril
CN Novocaptopril
CN S-Captopril
CN SA 333
CN SQ 14225
CN Tensiomin
CN Tensobon
CN Tensoprel

=> d que l21; d l21
L21 1 SEA FILE=REGISTRY ABB=ON PLU=ON 9015-82-1

L21 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **9015-82-1** REGISTRY
CN Carboxypeptidase, dipeptidyl, A (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ACE
CN ACE (enzyme)
CN Angiotensin I-converting enzyme
CN Angiotensin-1 converting enzyme

CN Angiotensin-converting enzyme
CN Angiotensin-converting enzyme I
CN Angiotension-converting enzyme
CN Carboxycathepsin
CN Carboxypeptidase Zace2
CN Dipeptidyl carboxypeptidase A
CN Dipeptidyl serine carboxypeptidase
CN E.C. 3.4.15.1
CN Endothelial cell peptidyl dipeptidase
CN Kininase II
CN Peptidase P
CN Peptidyl dipeptidase
CN Peptidyl dipeptidase A
CN Peptidyl dipeptidase-4
CN Peptidyl-dipeptidase A
CN Peptidyldipeptide hydrolase A
CN Vasopeptidase
CN Zinc metallopeptidase Zace1
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSNB, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
12461 REFERENCES IN FILE CA (1957 TO DATE)
55 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12491 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 11:33:14 ON 14 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 14 Jul 2003 VOL 139 ISS 3
FILE LAST UPDATED: 13 Jul 2003 (20030713/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d his

(FILE 'HOME' ENTERED AT 11:09:07 ON 14 JUL 2003)

FILE 'REGISTRY' ENTERED AT 11:09:15 ON 14 JUL 2003

```
                E ANGIOTENSIN II/CN
L1            1 S E3
                E ANGIOTENSIN CONVERTING ENZYME/CN
                E BENAZEPRIL/CN
                E BENAZEPRIL/CN
L2            2 S E3-4
                E CAPTOPRIL/CN
L3            1 S E3
                E CERONAPRIL/CN
L4            1 S E3
                E ENALAPRIL/CN
L5            1 S E3
                E FOSINOPRIL/CN
L6            1 S E3
                E IMIDAPRIL/CN
L7            1 S E3
L8            1 S E4
                E LISINOPIRL/CN
L9            1 S E4
                E MOEXIPRIL/CN
L10           1 S E3
L11           1 S E4
                E QUINAPRIL/CN
L12           2 S E3-4
                E RAMIPRIL/CN
L13           1 S E3
L14           1 S E5
                E TRANDOLAPRIL/CN
L15           2 S E4-5
                E PERINDOPRIL/CN
L16           2 S E4 OR E6
L17          19 S L2-L16
                E SARTAN/CN
                E SARATAN/CN
                E SARTAN/CN

     FILE 'HCAPLUS' ENTERED AT 11:13:58 ON 14 JUL 2003

     FILE 'REGISTRY' ENTERED AT 11:15:45 ON 14 JUL 2003

     FILE 'HCAPLUS' ENTERED AT 11:16:10 ON 14 JUL 2003
                E SARTAN/CT
L18       22665 S L1 OR ANGIOTENSIN II
L19        3346 S L18 (L) ANTAGONIS?
L20       10175 S ANGIOTENSIN CONVERT? ENZYME?

     FILE 'HCAPLUS' ENTERED AT 11:25:11 ON 14 JUL 2003

     FILE 'REGISTRY' ENTERED AT 11:25:32 ON 14 JUL 2003
L21           1 S 9015-82-1

     FILE 'HCAPLUS' ENTERED AT 11:25:38 ON 14 JUL 2003
L22        7583 S (L20 OR ACE) (L) INHIBIT?
L23       13350 S L22 OR L21
L24        7457 S L17
L25       17220 S L23 OR L24
L26         679 S L25 AND L19
L27       46585 S DEMENTIA OR MENTAL (L) (DISORDER OR DISEASE) OR SENIL?
L28           9 S L26 AND L27
L29          18 S SARTAN OR SARTAN/AB
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L30           1 S L29 AND L25
L31          17 S L29 NOT L30
                E ANDERSON C/AU
L32         938 S E3-60
                E ANDERSON CRAIG/AU
L33          35 S E3-11
                E YUSUF S/AU
L34         393 S E11 OR E3-9
                E SLEIGHT P/AU
L35          60 S E3-4
                E HILBRICH L/AU
L36           2 S E4
L37        1421 S L32-L36
L38           4 S L37 AND L25 AND L19

     FILE 'REGISTRY' ENTERED AT 11:32:20 ON 14 JUL 2003

     FILE 'HCAPLUS' ENTERED AT 11:33:14 ON 14 JUL 2003

=> d que nos 130
L2            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (BENAZEPRIL/CN OR "BENAZEPRIL
                  HYDROCHLORIDE"/CN)
L3            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CAPTOPRIL/CN
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CERONAPRIL/CN
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  ENALAPRIL/CN
L6            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  FOSINOPRIL/CN
L7            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  IMIDAPRIL/CN
L8            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "IMIDAPRIL HYDROCHLORIDE"/CN

L9            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  LISINOPRIL/CN
L10           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  MOEXIPRIL/CN
L11           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "MOEXIPRIL HYDROCHLORIDE"/CN

L12           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (QUINAPRIL/CN OR "QUINAPRIL
                  HYDROCHLORIDE"/CN)
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  RAMIPRIL/CN
L14           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RAMIPRIL HYDROCHLORIDE"/CN
L15           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("TRANDOLAPRIL HYDROCHLORIDE"
                  /CN OR TRANDOLAPRILAT/CN)
L16           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PERINDOPRIL EBUMINE"/CN OR
                  "PERINDOPRIL HYDROCHLORIDE"/CN
L17          19 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L2 OR L3 OR L4 OR L5 OR L6
                  OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR
                  L16)
L20       10175 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANGIOTENSIN CONVERT? ENZYME?/O
                  BI
L21           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  9015-82-1
L22        7583 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L20 OR ACE/OBI) (L) INHIBIT?/
                  OBI
L23       13350 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L21
L24        7457 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17
L25       17220 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 OR L24
L29          18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SARTAN/OBI OR SARTAN/AB
L30           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 AND L25


=> d que nos l29;d his l31
L29          18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SARTAN/OBI OR SARTAN/AB
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(FILE 'HCAPLUS' ENTERED AT 11:25:38 ON 14 JUL 2003)
L31 17 S L29 NOT L30

=> d .ca l30 ;d .ca l31 1-17

L30 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:138724 HCAPLUS
DOCUMENT NUMBER: 136:288811
TITLE: The course of potassium and creatinine in patients with severe heart failure by use of **ACE inhibitors** combined with AT1 antagonists either eprosartan either telmisartan
AUTHOR(S): Gremmler, B.; Kisters, K.; Kunert, M.; Schleiting, H.; Ulbricht, L. J.
CORPORATE SOURCE: Department of Cardiology, Marienhospital Bottrop, Bottrop, D-46236, Germany
SOURCE: Trace Elements and Electrolytes (2002), 19(1), 1-5
CODEN: TEELEO; ISSN: 0946-2104
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The efficacy of ACE inhibitor therapy is well documented in the treatment of chronic heart failure. As pharmacol. mechanisms of ACE inhibition and angiotensin II AT1 receptor antagonists differ, an addnl. pos. effect concerning left ventricular function can be expected in combining both classes of drugs. In view of the fact that both drugs influence the RAA system, a change concerning the level of potassium and creatinine could be possible by using the combined therapy with **sartans** and ACE inhibitors. Forty-five patients (69.1.+-.7.9 yr) with advanced chronic heart failure (NYHA Class III) receiving long-term medication with digitalis, diuretics and ACE inhibitors were randomized after clin. recompensation to either eprosartan (n = 15; 510.+-.120 mg/d) or placebo (n = 15), according to a blinded protocol. Addnl., a prospective study by using telmisartan (n = 15; 66.9.+-.14.4 mg) was performed. The course of potassium and creatinine was detd. at baseline and after 9.8.+-.2.2 days of study medication treatment. Hemodynamic measurements by impedance cardiog. were simultaneously performed. In all groups, a slight increase of potassium level was obsd. (control group: mean 4.36.+-.0.45 mval/l, end of study 4.47.+-.0.40 mval/l; eprosartan group initially mean 4.28.+-.0.43 mval/l vs. 4.50.+-.0.25 mval/l). Only in the telmisartan group was the slight increase of potassium statistically significant (mean 4.1.+-.0.38 mval/l vs. 4.48.+-.0.3 mval at end of study; p = 0.01). In all groups, anal. of serum creatinine revealed no significant change during the observation period. Addnl., treatment with **sartans** furthermore resulted in an improvement of cardiac output. There was an increase in cardiac output from 2.31.+-.0.6 to 3.04.+-.0.98 l/min (p = 0.03) in the eprosartan group and from 2.2.+-.0.49 to 2.77.+-.0.74 l/min (p = 0.003) in the telmisartan group, but no change in the control group was obsd. The addnl. treatment with AT1 receptor antagonists, given to severe heart failure patients, who received digitalis, diuretics, ACE inhibitors and mostly .beta.-blockers, resulted in a beneficial effect by increasing cardiac output. Under the combined therapy, a slight increase of serum potassium level was obsd. Furthermore, no relevant change of serum creatinine was seen.
CC 1-8 (Pharmacology)
ST potassium creatinine heart failure **ACE inhibitor**; AT1 antagonist eprosartan telmisartan
IT Heart

(cardiac output; potassium and creatinine levels in patients with severe heart failure using **ACE inhibitors** combined with AT1 antagonists, eprosartan or telmisartan)

IT Heart, disease
(failure, chronic; potassium and creatinine levels in patients with severe heart failure using **ACE inhibitors** combined with AT1 antagonists, eprosartan or telmisartan)

IT Angiotensin receptor antagonists
Cardiovascular system
Circulation
Human
Renin-angiotensin system
(potassium and creatinine levels in patients with severe heart failure using **ACE inhibitors** combined with AT1 antagonists, eprosartan or telmisartan)

IT **9015-82-1, Angiotensin-converting enzyme**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; potassium and creatinine levels in patients with severe heart failure using **ACE inhibitors** combined with AT1 antagonists, eprosartan or telmisartan)

IT 60-27-5, Creatinine 7440-09-7, Potassium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(potassium and creatinine levels in patients with severe heart failure using **ACE inhibitors** combined with AT1 antagonists, eprosartan or telmisartan)

IT 133040-01-4, Eprosartan 144701-48-4, Telmisartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potassium and creatinine levels in patients with severe heart failure using **ACE inhibitors** combined with AT1 antagonists, eprosartan or telmisartan)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:428018 HCAPLUS
TITLE: Chlorine-36 and 14C chronology support a limited last glacial maximum across central Chukotka, northeastern Siberia, and no Beringian ice sheet
AUTHOR(S): Brigham-Grette, Julie; Gualtieri, Lyn M.; Glushkova, Olga Yu.; Hamilton, Thomas D.; Mostoller, David; Kotov, Anatoly
CORPORATE SOURCE: Department of Geosciences, University of Massachusetts, Amherst, MA, 01003, USA
SOURCE: Quaternary Research (2003), 59(3), 386-398
CODEN: QRESAV; ISSN: 0033-5894
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Pekulney Mountains and adjacent Tanyurer River valley are key regions for examg. the nature of glaciation across much of northeast Russia. Twelve new cosmogenic isotope ages and 14 new radiocarbon ages in concert with morphometric analyses and terrace stratigraphy constrain the timing of glaciation in this region of central Chukotka. The **Sartan** Glaciation (Last Glacial Maximum) was limited in extent in the Pekulney Mountains and dates to .apprx.20,000 yr ago. Cosmogenic isotope ages >

30,000 yr as well as non-finite radiocarbon ages imply an estd. age no younger than the Zyryan Glaciation (early Wisconsinan) for large sets of moraines found in the central Tanyurer Valley. Slope angles on these loess-mantled ridges are less than a few degrees and crest widths are an order of magnitude greater than those found on the younger **Sartan** moraines. The most extensive moraines in the lower Tanyurer Valley are most subdued implying an even older, probable middle Pleistocene age. This research provides direct field evidence against Grosswald's Beringian ice-sheet hypothesis.
CC 53 (Mineralogical and Geological Chemistry)

L31 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:341871 HCAPLUS
TITLE: Neonatal Acute Renal Failure Secondary to Maternal Exposure to Telmisartan, Angiotensin II Receptor Antagonist
AUTHOR(S): Pietrement, Christine; Malot, Lilia; Santerne, Brigitte; Roussel, Bernard; Motte, Jacques; Morville, Patrice
CORPORATE SOURCE: Department of Pediatrics, American Memorial Hospital, Reims, Fr.
SOURCE: Journal of Perinatology (2003), 23(3), 254-255
CODEN: JOPEEI; ISSN: 0743-8346
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fetal and neonatal toxic effects of angiotensin II receptor antagonists have been described in animals and humans. Five cases of fetal or neonatal deaths have been reported following maternal use of **sartans** for hypertension. We report a case of neonatal transient renal failure following telmisartan therapy during pregnancy. This class of antihypertensive drugs should be avoided during pregnancy and breastfeeding.Journal of Perinatol. (2003) 23, 254-255.
CC 1 (Pharmacology)

L31 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:326026 HCAPLUS
TITLE: Design and synthesis of novel antihypertensive drugs
AUTHOR(S): Moutevelis-Minakakis, P.; Gianni, M.; Stougiannou, H.; Zoumpoulakis, P.; Zoga, A.; Vlahakos, A. D.; Iliodromitis, E.; Mavromoustakos, T.
CORPORATE SOURCE: Department of Chemistry, University of Athens, Zographou, Athens, 15771, Greece
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(10), 1737-1740
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB AT1 antagonists constitute a new generation of drugs for the treatment of hypertension and are designed and synthesized to mimic the C-terminal segment of Angiotensin II (Ang II) and to block its binding action on AT1 receptor. For this reason, the conformational anal. of Ang II and its derivs. as well as the AT1 antagonists belonging to **SARTANs** class of mols. were studied. Such studies offer the possibility to reveal the stereoelectronic factors responsible for bioactivity of AT1 antagonists and to design and synthesize new analogs with better pharmacol. and financial profiles. An example of a novel synthetic non-peptide mol. is given which mimics the His6-Pro7-Phe8 part of Ang II and is based on the (S)-pyroglutamic acid.

CC 34 (Amino Acids, Peptides, and Proteins)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:481399 HCAPLUS
DOCUMENT NUMBER: 138:18993
TITLE: Pharmaceutical chemistry of **sartans**
AUTHOR(S): Takacsne Novak, Krisztina; Hankone Hragyel, Zsuzsanna
CORPORATE SOURCE: Gyogyszereszeti Kemiai Intezet, Semmelweis Egyetem, Budapest, 1092, Hung.
SOURCE: Gyogyszereszet (2002), 46(3), 131-140
CODEN: GYOGAI; ISSN: 0017-6036
PUBLISHER: Gyogyszereszet Szerkesztosege
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Hungarian
AB A review. The study discusses the new group of antihypertensives, namely the angiotensin II receptor antagonists (**sartans**). Topics included are: structure-property relationship, drug activity, pharmacol., metab., application, anal. methods.
CC 1-0 (Pharmacology)
ST review antihypertensive **sartan** angiotensin receptor antagonist
IT Angiotensin receptor antagonists
(angiotensin II, **sartans**; pharmaceutical chem. of **sartans**)
IT Antihypertensives
Molecular structure-property relationship
(pharmaceutical chem. of **sartans**)

L31 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:426884 HCAPLUS
DOCUMENT NUMBER: 137:154714
TITLE: Suzuki-Miyaura Cross-Coupling Reactions Mediated by Palladium/Imidazolium Salt Systems
AUTHOR(S): Grasa, Gabriela A.; Viciu, Mihai S.; Huang, Jinkun; Zhang, Chunming; Trudell, Mark L.; Nolan, Steven P.
CORPORATE SOURCE: Department of Chemistry, University of New Orleans, New Orleans, LA, 70148, USA
SOURCE: Organometallics (2002), 21(14), 2866-2873
CODEN: ORGND7; ISSN: 0276-7333
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:154714
AB Nucleophilic N-heterocyclic carbenes (NHC) were used as ancillary ligands in Pd-mediated Suzuki-Miyaura cross-coupling reactions involving aryl chlorides or aryl triflates with arylboronic acids. The scope of the coupling process using Pd(0) or Pd(II) sources and an imidazolium salt in the presence of a base, Cs2CO3, was tested using various substrates. The Pd(OAc)2 or Pd2(dba)3/IMes.HCl (2 = 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, where IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) system presents very high activity with respect to electron-neutral and electron-rich aryl chlorides. E.g., the Pd(OAc)2/IMes.HCl catalyzed reaction of PhB(OH)2 with p-MeC6H4Cl in presence of Cs2CO3 as base at 80.degree. (2.5 h) in dioxane gave p-MeC6H4Ph in 99% yield. The ligand IPr.HCl (3 = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, where IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) is also effective for the Suzuki-Miyaura cross-coupling involving a wide spectrum of aryl chlorides and aryl triflates. The general protocol developed was applied

successfully to the synthesis of an antiinflammatory drug (Fenbufen) and to a key intermediate in the synthesis of **sartans**. Mechanistically, Pd-to-ligand ratio studies support an active Pd species bearing b one nucleophilic carbene ligand.

CC 25-2 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 22, 29, 67

ST Suzuki Miyaura cross coupling reaction palladium imidazolium salt mediated; aryl chloride arylboronic acid palladium mediated Suzuki Miyaura coupling; aryl triflate arylboronic acid palladium mediated Suzuki Miyaura coupling; heterocyclic carbene ancillary ligand palladium mediated Suzuki Miyaura coupling; Fenbufen antiinflammatory drug synthesis palladium mediated Suzuki Miyaura coupling; palladium mediated Suzuki Miyaura coupling chlorobenzonitrile arylboronic **sartan** synthesis; **sartan** synthesis palladium imidazolium salt mediated Suzuki Miyaura coupling

IT Synthons
(nucleophilic N-heterocyclic carbenes as ancillary ligands in palladium-mediated Suzuki-Miyaura cross-coupling reactions involving aryl chlorides with arylboronic acids for strategic intermediate in prepn. of **sartans**)

REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:133949 HCAPLUS
DOCUMENT NUMBER: 137:119044
TITLE: Structure elucidation and conformational properties of eprosartan a non peptide Angiotensin II AT1 antagonist
AUTHOR(S): Zoumpoulakis, Panagiotis; Grdadolnik, Simona Golic; Matsoukas, John; Mavromoustakos, Thomas
CORPORATE SOURCE: Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Athens, 11635, Greece
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2002), 28(1), 125-135
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel approach to treat hypertension is to interfere with the Renin-Angiotensin system (RAS) by blocking the binding of vasoconstrictive hormone Angiotensin II to the AT1 receptor site. This approach led to the beneficial drug losartan (COZAAR) and other similar in structure to the antihypertensive drugs (**sartans**). In an effort to compare the stereoelectronic features of pharmacophoric segments of the different **sartans**, a research activity was initiated in our lab. related to the conformational properties of these drugs. In a previous study, the structural features which det. the pharmacophoric segments of losartan were examd. In this study, the conformational properties of eprosartan (TEVETEN), a drug with fewer side effects, were examd. In addn., the superimposition ability of losartan and eprosartan with the peptide antagonist sarmesin was studied.

CC 1-3 (Pharmacology)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:128761 HCAPLUS
DOCUMENT NUMBER: 137:179602
TITLE: Comparison of valsartan with candesartan on their

possible protection from atherosclerosis
AUTHOR(S): Mueck, A. O.; Seeger, H.; Heuberger, W.; Wallwiener, D.
CORPORATE SOURCE: Department of Obstetrics and Gynaecology, University-Hospital, Tuebingen, 72076, Germany
SOURCE: Journal of Clinical and Basic Cardiology (2001), 4(4), 297-299
CODEN: JCBCFT; ISSN: 1561-2775
PUBLISHER: Krause & Pachernegg GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It is well appreciated that AT1-antagonists do diminish long-term effects of angiotensin on the blood pressure which are regarded as detrimental. In the present in vitro expts. we compared the efficacies of valsartan and candesartan in preventing neg. outcomes of angiotensin effect on markers of endothelial function and on proliferation of smooth muscle cells. Angiotensin II (10 .mu.M) induced a decrease in the concn. of endothelial-derived nitric oxide synthase and increases the concn. of the vasoconstrictor endothelin, the procoagulatory substance plasminogen-activator-inhibitor-1 (PAI-1) and of the precursor of the matrix-metalloproteinase 1 (MMP-1) in endothelial cell cultures from human coronary arteries. These changes were completely prevented by the addn. of 10 .mu.M of valsartan or candesartan and partially by the addn. of lower concns. of the **sartans**, ie 1 .mu.M and 0.1 .mu.M. No significant difference was obsd. in the effect of the two **sartans**. The angiotensin II-induced increase of coronary artery smooth muscle cell proliferation was also completely prevented by the addn. of 10 .mu.M of the **sartans**. These results suggest that **sartans** may class-specifically inhibit neg. actions of angiotensin II on endothelial function and smooth muscle cell proliferation. Thus **sartans** may be able to prevent the initiation and progression of atherosclerosis.
CC 1-8 (Pharmacology)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:140680 HCAPLUS
DOCUMENT NUMBER: 134:175822
TITLE: Angiotensin signaling and receptor types in teleost fish
AUTHOR(S): Russell, Michael J.; Klemmer, Alison M.; Olson, Kenneth R.
CORPORATE SOURCE: Indiana University School of Medicine, South Bend Center for Medical Education, University of Notre Dame, Notre Dame, IN, 46556, USA
SOURCE: Comparative Biochemistry and Physiology, Part A: Molecular & Integrative Physiology (2001), 128A(1), 41-51
CODEN: CBPAB5; ISSN: 1095-6433
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 47 refs. Despite advances characterizing mammalian angiotensin receptors, the phylogeny of fish angiotensin receptors remains unclear. Three aspects of receptor function: (1) the nature of the ligand; (2) the second messenger system activated by it; and (3) the pharmacol. profile of specific antagonists, are examd. to provide insight into the fish receptor. The octapeptide sequences of fish and mammalian angiotensin II (ANG II) are nearly homologous, differing only at the 1st

and 5th residues. Both peptides are almost equally efficacious and equipotent in heterologous systems and both contain key agonist switches Tyr4 and Phe8 necessary to activate mammalian AT1-type receptors. ANG II increases inositol trisphosphate prodn., and elevates intracellular calcium in fish tissues consistent with activation of the AT1 receptor. However, the specific mammalian **sartan**-type AT1 antagonists, e.g. losartan, produce inconsistent results in fish often acting as partial agonists, or inhibiting only at elevated concns. Because **sartans** and ANG II act at distinct sites on the AT1 receptor, we propose that the teleost receptor is an AT1-type receptor that is fairly well conserved with respect to both the ANG binding site and coupling to the second messenger system, whereas the **sartan** binding site has been poorly conserved. The evidence for non-AT1 type ANG II receptors in teleosts is limited. Mammalian AT2 receptor antagonists are generally ineffective but may block at elevated, non-specific doses. Truncated ANG II fragments, ANG III, and ANG IV, are often less potent than ANG II, however, their receptors have not been examd. Preliminary studies in trout indicate that angiotensin 1-7 may have a mild vasodilatory effect; addnl. work is needed to det. if non-AT1-type receptors are involved.

CC 12-0 (Nonmammalian Biochemistry)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:849402 HCAPLUS
DOCUMENT NUMBER: 134:131025
TITLE: AMS 14C chronology of woolly mammoth (Mammuthus primigenius Blum.) remains from the Shestakovo upper Paleolithic site, western Siberia: timing of human-mammoth interaction
AUTHOR(S): Zenin, V. N.; Van der Plicht, J.; Orlova, L. A.; Kuzmin, Y. V.
CORPORATE SOURCE: Institute of Archaeology and Ethnography, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, 630090, Russia
SOURCE: Nuclear Instruments & Methods in Physics Research, Section B: Beam Interactions with Materials and Atoms (2000), 172, 745-750
CODEN: NIMBEU; ISSN: 0168-583X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of accelerator mass spectrometry (AMS) 14C dates from the upper paleolithic site of Shestakovo, southwestern Siberia, is presented. The 14C ages range between 21 and 26 ka BP, corresponding to the so-called **Sartan** Glacial and Karginian Interglacial in Siberia. The majority of dates are from woolly mammoth bones, obtained from several discrete cultural layers, and range from ca. 25,700 to 21,600 BP. One charcoal date, ca. 23,300 BP, pinpoints the timing of at least one phase of site occupation by humans. The overlap of this date with the mammoth bone dates shows clearly that paleolithic people scavenged bones from natural death accumulations near the site. Mammoth hunting was most probably of limited scale. Conventional 14C dates from Shestakovo are also discussed.

CC 20-3 (History, Education, and Documentation)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:641100 HCAPLUS

DOCUMENT NUMBER: 134:94991
TITLE: A review on telmisartan: A novel, long-acting angiotensin II-receptor antagonist
AUTHOR(S): Wienen, Wolfgang; Entzeroth, Michael; Van Meel, Jacobus C. A.; Stangier, Joachim; Busch, Ulrich; Ebner, Thomas; Schmid, Jochen; Lehmann, Horst; Matzek, Kandace; Kempthorne-Rawson, Joan; Gladigau, Volker; Hauel, Norbert H.
CORPORATE SOURCE: Departments of Chemical and Pharma Research, Boehringer Ingelheim, Biberach, D-88397, Germany
SOURCE: Cardiovascular Drug Reviews (2000), 18(2), 127-156
CODEN: CDREEA; ISSN: 0897-5957
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 67 refs. Telmisartan is a potent, long-lasting, nonpeptide antagonist of the angiotensin II type-1 (AT1) receptor that is indicated for the treatment of essential hypertension. It selectively and insurmountably inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. Very high lipophilicity, a unique feature of telmisartan, coupled with a high vol. of distribution, indicate that the compd. offers the clin. important advantage of good tissue penetration. Telmisartan is not a prodrug and has a longer terminal elimination half-life than other com. available **sartans** (.apprx.24 h), making it suitable for once-daily dosing. The compd. is not metabolized by cytochrome P 450 isoenzymes and has a low risk for P 450-based drug interactions. In animal models, telmisartan exhibits pronounced cardioand reno-protective effects in animals with severe, essential hypertension. In clin. studies, telmisartan shows comparable antihypertensive activity to members of other major antihypertensive classes, such as ACE inhibitors, beta blockers and calcium antagonists. These trials have confirmed the placebo-like safety and tolerability of telmisartan in hypertensive patients. Based on these data, telmisartan offers advantages over other **sartans** and represents an important new treatment option for hypertension.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:301824 HCAPLUS
DOCUMENT NUMBER: 133:290662
TITLE: In vitro inhibition screening of human hepatic P450 enzymes by five angiotensin-II receptor antagonists
AUTHOR(S): Taavitsainen, P.; Kiukaanniemi, K.; Pelkonen, O.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Oulu, FIN-90014, Finland
SOURCE: European Journal of Clinical Pharmacology (2000), 56(2), 135-140
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: Metabolic interactions at the level of drug-metabolizing enzymes are important for drug therapy. We investigated potential interactions of losartan, irbesartan, valsartan, eprosartan and candesartan with cytochrome P450 (CYP) enzymes in human liver microsomes. Methods: In incubations with human liver microsomes in vitro, the inhibitory potency of angiotensin-II receptor antagonists (**sartans**) on CYP-specific model activities were compared by measuring the IC50

and, with respect to more potent inhibition, Ki values. Results: None of the five **sartans** inhibited CYP2A6-, CYP2D6- or CYP2E1-assocd. activities (coumarin 7-hydroxylation, dextromethorphan O-demethylation and chlorzoxazone 6-hydroxylation, resp.) to any significant extent. Losartan and irbesartan inhibited the CYP2C9-assocd. tolbutamide methylhydroxylation more potently (Ki values 4.1 .mu.M and 24.5 .mu.M), than valsartan, candesartan or eprosartan (Ki values 135 .mu.M, 155 .mu.M and >1000 .mu.M, resp.). Losartan and irbesartan inhibited CYP1A2- and CYP3A4-assocd. activities (ethoxyresorufin O-deethylation and testosterone 6.beta.-hydroxylation) with relatively weak affinities (IC50 values between 200 .mu.M and 500 .mu.M). CYP2C19-assocd. S-mephenytoin 4'-hydroxylation activity was inhibited by losartan (IC50 value 138 .mu.M) and much less or not at all by the other **sartans** tested. Conclusion: All **sartans** except eprosartan have at least some affinity for CYP2C9, but only losartan has an affinity for CYP2C19. Losartan and irbesartan have modest affinity for CYP1A2 and CYP3A4. This would suggest that the theor. potential for drug interactions is likely to be quite low, with the possible exceptions of losartan and irbesartan for CYP2C9. Based on these findings, further studies on the interaction potential of losartan and irbesartan are warranted.

CC 1-4 (Pharmacology)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:64536 HCAPLUS
DOCUMENT NUMBER: 133:3
TITLE: Neurohormonal modulation in cardiovascular disease
AUTHOR(S): Unger, Thomas
CORPORATE SOURCE: Institute of Pharmacology, Christian Albrechts University, Kiel, 24105, Germany
SOURCE: American Heart Journal (2000), 139(1, Pt. 2), S2-S8
CODEN: AHJOA2; ISSN: 0002-8703
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review and discussion with 50 refs. The renin-angiotensin system (RAS) is one of the oldest known hormone systems. Its effector hormone, angiotensin (Ang) II, acts through 2 receptor subtypes, AT1 and AT2. Most physiol. effects of Ang II, including vasoconstriction, renal salt and water retention, aldosterone and vasopressin release, and sympathetic facilitation, are mediated by AT1. Recent data, however, suggest that Ang II also contributes to cell proliferation, left ventricular hypertrophy, vascular media hypertrophy, neointima formation in atherosclerosis, and nephrosclerosis by stimulation of AT1 receptors. AT2 receptors are assocd. with antiproliferation, cell differentiation and development, tissue regeneration, and apoptosis. They also antagonize AT1 receptor-mediated effects, which suggests that the ratio of angiotensin receptors expressed on a particular cell can det. the net effect of Ang II. Selective AT1 receptor antagonists (**sartans**) have been used to treat several million hypertensive patients worldwide. These agents offer a powerful therapeutic alternative to angiotensin-converting enzyme (ACE) inhibitors, which reduce the generation of Ang II. Conversely, AT1 receptor antagonists block the RAS by acting on cellular angiotensin receptors and do not interfere with the breakdown of kinins. These medications inhibit the RAS more completely than do the ACE inhibitors because their action is independent of Ang II-generating pathways. At the same time, early, preliminary data suggest that AT1 receptor antagonists offer target-organ protection similar to that provided by the ACE inhibitors. Because AT2 receptors are left unopposed and Ang II levels

are increased with AT1 receptor antagonist treatment, it is important to understand the function of AT2 to fully appreciate the mechanisms of action of AT1 receptor antagonists, esp. their potential for target-organ protection.
CC 1-0 (Pharmacology)
Section cross-reference(s): 14
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:501314 HCAPLUS
DOCUMENT NUMBER: 131:306587
TITLE: Angiotensin II receptor antagonists: an emerging new class of cardiovascular therapeutics
AUTHOR(S): Timmermans, Pieter B. M. W. M.
CORPORATE SOURCE: Pharmacology and Preclinical Development Department, Tularik Inc., South San Francisco, CA, 94080, USA
SOURCE: Hypertension Research (1999), 22(2), 147-153
CODEN: HRESE4; ISSN: 0916-9636
PUBLISHER: Japanese Society of Hypertension
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 26 refs. Acceptance of the notion that physiol. specific interruption of the renin-angiotensin-aldosterone system (RAAS) is of considerable therapeutic benefit in the treatment of hypertension and congestive heart failure has generated great interest in the search for novel pharmacol. inhibitors. The RAAS is expressed at the whole body, organ/tissue and cellular level through the action of the octapeptide angiotensin II (Ang II), the primary effector mol. of the RAAS. The availability of selective, potent, orally active and long-acting nonpeptide Ang II type 1 (AT1) receptor antagonists provided the opportunity to obtain the benefits of selectively blocking the RAAS at the level of the AT1 receptor that mediates most, if not all, of the important actions of Ang II, and avoid the nonspecificity of the Ang I converting enzyme (ACE) inhibitors. Losartan was the first, but by no means remained the only nonpeptide AT1 receptor antagonist. Numerous other "**sartans**" have emerged in the past several years and successfully completed clin. development. With the exception of Eprosartan, all others, i.e., Candesartan, Irbesartan, Saprisartan, Tasosartan, Telmisartan, Valsartan and Zolasartan, are based on modifications of Losartan's prototypic chem. structure. AT1 receptor antagonists represent the newest addn. to the arsenal of cardiovascular therapeutics. The predominant role of the AT1 receptor in mediating the pathophysiol. role of Ang II underlies the effectiveness of this novel class of agents to lower arterial blood pressure, reduce pre- and afterload, inhibit sympathetic nervous system activity and prevent cardiovascular hypertrophy and cardiac failure induced by inappropriate control of the RAAS.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:496269 HCAPLUS
DOCUMENT NUMBER: 131:138713
TITLE: Non-peptide angiotensin type 1 receptor antagonists in the treatment of hypertension
AUTHOR(S): Birkenhager, Willem H.; De Leeuw, Peter W.
CORPORATE SOURCE: Erasmus University, Rotterdam, Neth.
SOURCE: Journal of Hypertension (1999), 17(7), 873-881
CODEN: JOHYD3; ISSN: 0263-6352

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 85 refs. Angiotensin II (Ang II) acts at the cellular level on two receptor subtypes: the AT1 receptor which can be blocked by losartan and its analogs (the '**sartan** family'), and the AT2 receptor that does not react with the above antagonists but which can be blocked by different compds., such as PD123319. AT1 receptor blockade has proven to be a highly effective means of interference with the renin-angiotensin system (RAS) and hence of reducing high blood pressure. As a result of the terminal blockade of the RAS cascade, circulating Ang II levels tend to rise two- to threefold. The free access of such enhanced levels to uninhibited AT2 receptors may be clin. relevant, as argued in the present review. The most extensive exptl. and clin. experience with AT1 receptor blockade so far has been obtained with the pioneer drug losartan, although major contributions have also been made on candesartan cilexetil, irbesartan and valsartan. All of these four drugs have been instrumental in substantial clin. trials, serving as sources of information in the clin. oriented part of this review. AT1 receptor blocking drugs generally provide a relatively gradual decrease in blood pressure, which is comparable to that obtained with conventional anti-hypertensive drugs. Clin. trials reveal an astounding lack of drug-related adverse effects, scoring even better than placebo in terms of frequencies and sometimes patterns. The trough/peak ratio on single dosages seems to have been mastered, particularly with the second generation of AT1 receptor blockers, as is evident from 24 h ambulatory blood pressure monitoring. Combination with low-dose thiazide regimens is well established. Intermediate endpoints (micro-albuminuria and left ventricular hypertrophy) appear to be controllable. Morbid cardiovascular sequelae are currently under study in comparison with .beta.- and calcium channel blockade.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:488142 HCAPLUS
DOCUMENT NUMBER: 131:138686
TITLE: Angiotensin II receptor antagonists and hypertension
AUTHOR(S): Mimran, Albert; Ribstein, Jean; DuCailar, Guilhem
CORPORATE SOURCE: Department of Medicine, Centre Hospitalier Universitaire, Montpellier, Fr.
SOURCE: Clinical and Experimental Hypertension (1999), 21(5 & 6), 847-858
CODEN: CEHYER; ISSN: 1064-1963
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 50 refs. Over recent years, a no. of imidazole derivs. that specifically bind to the angiotensin II type 1 receptor, thereafter called **sartans**, have been developed and made available to the clinician. Whether targeting antihypertensive treatment with such a high specificity within the renin cascade may carry major clin. advantage over inhibiting angiotensin converting-enzyme remains to be demonstrated. In short-term studies, the efficacy of these drugs at reducing blood pressure was similar to that of established comparators, whereas overall side effect profile was comparable to that of placebo.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:450331 HCAPLUS
DOCUMENT NUMBER: 131:111191
TITLE: Valsartan inhibits angiotensin II-stimulated proliferation of smooth muscle cells from human coronary artery
AUTHOR(S): Mueck, A. O.; Seeger, H.; Lippert, T. H.
CORPORATE SOURCE: Section Clinical Pharmacology, Dep. Obstetrics Gynecology, Univ. Tubingen, Tubingen, D-72076, Germany
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (1999), 37(7), 365-366
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiotensin II is involved in the pathogenesis of atherosclerosis by inducing hyperproliferation of vascular smooth muscle cells. Little is known whether the **sartans** can inhibit the angiotensin-stimulated proliferation of smooth muscle cells. The effect of valsartan on the angiotensin II-stimulated proliferation of smooth muscle cells from human coronary artery was investigated. Angiotensin II increased cell proliferation by about 30% at a concn. of 10-6 M without changes at the lower concns. 10-7 and 10-8 M. Valsartan at the dosages 10-8 to 10-6 M had no effect on serum-stimulated proliferation. Valsartan at the dosages 10-6 and 10-7 M inhibited the cell proliferation induced by 10-6 M angiotensin. Valsartan may prevent atherosclerosis by inhibiting angiotensin-induced vascular smooth muscle cell proliferation.
CC 1-8 (Pharmacology)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:731861 HCAPLUS
DOCUMENT NUMBER: 129:326157
TITLE: Pharmacology of angiotensin receptors and AT1 receptor blockers
AUTHOR(S): Chung, O.; Unger, T.
CORPORATE SOURCE: Inst. Pharmacology, Univ. Kiel, Kiel, D-24105, Germany
SOURCE: Basic Research in Cardiology (1998), 93(Suppl. 2), 15-23
CODEN: BRCAB7; ISSN: 0300-8428
PUBLISHER: Dr. Dietrich Steinkopff Verlag GmbH & Co. KG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review is given with 80 refs. on angiotensin II (ANGII) receptors and AT1 receptor blockers including the topics development of ANGII receptor binding substances, ANGII receptor subtypes, what AT1 receptor antagonists have (and do not have) in common, losartan, valsartan, irbesartan, candesartan-cilexetil/candesartan, and eprosartan.
CC 2-0 (Mammalian Hormones)
ST review angiotensinII receptor AT1 blocker **sartan**

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=> d que l38
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ANGIOTENSIN II"/CN
L2             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (BENAZEPRIL/CN OR "BENAZEPRIL
                  HYDROCHLORIDE"/CN)
L3             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CAPTOPRIL/CN
L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CERONAPRIL/CN
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  ENALAPRIL/CN
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  FOSINOPRIL/CN
L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  IMIDAPRIL/CN
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "IMIDAPRIL HYDROCHLORIDE"/CN

L9             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  LISINOPRIL/CN
L10            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  MOEXIPRIL/CN
L11            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "MOEXIPRIL HYDROCHLORIDE"/CN

L12            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (QUINAPRIL/CN OR "QUINAPRIL
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L13            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  RAMIPRIL/CN
L14            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RAMIPRIL HYDROCHLORIDE"/CN
L15            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("TRANDOLAPRIL HYDROCHLORIDE"
                  /CN OR TRANDOLAPRILAT/CN)
L16            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PERINDOPRIL EBUMINE"/CN OR
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L17           19 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L2 OR L3 OR L4 OR L5 OR L6
                  OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR
                  L16)
L18        22665 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR ANGIOTENSIN II/OBI
L19         3346 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18 (L) ANTAGONIS?/OBI
L20        10175 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANGIOTENSIN CONVERT? ENZYME?/O
                  BI
L21            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  9015-82-1
L22         7583 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L20 OR ACE/OBI) (L) INHIBIT?/
                  OBI
L23        13350 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L21
L24         7457 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17
L25        17220 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 OR L24
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                 C A"/AU OR "ANDERSON C A F"/AU OR "ANDERSON C A JR"/AU OR
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                 BERTIL"/AU OR "ANDERSON C C"/AU OR "ANDERSON C CLARINE"/AU OR
                 "ANDERSON C CLEMENT"/AU OR "ANDERSON C COLLINS"/AU OR "ANDERSON
                  C D"/AU OR "ANDERSON C E"/AU OR "ANDERSON C E JR"/AU OR
                 "ANDERSON C ERIC"/AU OR "ANDERSON C F"/AU OR "ANDERSON C F
                 L"/AU OR "ANDERSON C G"/AU OR "ANDERSON C GEO"/AU OR "ANDERSON
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                 "ANDERSON C N"/AU OR "ANDERSON C O"/AU OR "ANDERSON C P"/AU OR
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                 OR "ANDERSON C S"/AU OR "ANDERSON C T"/AU OR "ANDERSON C
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                 OR "ANDERSON C V"/AU OR "ANDERSON C V D R"/AU OR "ANDERSON C
                 W"/AU OR "ANDERSON C W N"/AU OR "ANDERSON C W P"/AU OR
                 "ANDERSON C WILLIAM"/AU OR "ANDERSON C WM"/AU OR "ANDERSON C
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L33          35 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("ANDERSON CRAIG"/AU OR
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                CRAIG D"/AU OR "ANDERSON CRAIG E"/AU OR "ANDERSON CRAIG L"/AU
                OR "ANDERSON CRAIG M"/AU OR "ANDERSON CRAIG P"/AU OR "ANDERSON
                CRAIG S"/AU)
L34         393 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "YUSUF SALIM"/AU OR ("YUSUF
                S"/AU OR "YUSUF S D"/AU OR "YUSUF S M"/AU OR "YUSUF S MOHAMMAD"
                /AU OR "YUSUF S O"/AU OR "YUSUF S W"/AU OR "YUSUF S WAMIQUE"/AU
                )
L35          60 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("SLEIGHT P"/AU OR "SLEIGHT
                PETER"/AU)
L36           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "HILBRICH LUTZ"/AU
L37        1421 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L32 OR L33 OR L34 OR L35 OR
                L36)
L38           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 AND L25 AND L19

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↳ inventor search

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L38  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2001:167788  HCAPLUS
DOCUMENT NUMBER:          134:188210
TITLE:                    Use of inhibitors of the renin-angiotensin system in
                          the prevention of cardiovascular events
INVENTOR(S):              Schoelkens, Bernward; Bender, Norbert; Rangoonwala,
                          Badrudin; Yusuf, Salim
PATENT ASSIGNEE(S):       Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE:                   PCT Int. Appl., 33 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2001015674      A2   20010308       WO 2000-EP8461    20000830
     WO 2001015674      A3   20020328
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     BR 2000013704      A    20020507       BR 2000-13704     20000830
     EP 1216038         A2   20020626       EP 2000-965906    20000830
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL
     EE 200200086       A    20030415       EE 2002-86        20000830
     BG 106360          A    20021031       BG 2002-106360    20020128
     NO 2002000978      A    20020418       NO 2002-978       20020227
PRIORITY APPLN. INFO.:                    US 1999-151436P   P  19990830
                                          WO 2000-EP8461    W  20000830
AB   The invention discloses the use of an inhibitor of the renin-angiotensin
     system, or a pharmaceutically acceptable deriv. thereof, optionally
     together with an other antihypertensive, a cholesterol lowering agent, a
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diuretic, or aspirin, in the manuf. of a medicament for the prevention of cardiovascular events; a method of preventing cardiovascular events comprising administering to a patient in need of such prevention an effective amt. of an inhibitor of the renin angiotensin system, or a pharmaceutically acceptable deriv. thereof, optionally together with an other antihypertensive, a cholesterol lowering agent, a diuretic or aspirin; and a combination product contg. an inhibitor of the renin-angiotensin system, or a pharmaceutically acceptable deriv. thereof, and a cholesterol lowering agent.

IC ICM A61K031-00

CC 1-8 (Pharmacology)

IT Angiotensin receptor **antagonists**
(**angiotensin II**; renin-angiotensin system inhibitor for prevention of cardiovascular event, and use with other agents)

IT **9015-82-1**, **Angiotensin converting enzyme**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; renin-angiotensin system **inhibitor** for prevention of cardiovascular event, and use with other agents)

IT 50-78-2, Aspirin 39698-78-7, Saralasin acetate **62571-86-2**, Captopril 74258-86-9, Alacepril 75330-75-5, Lovastatin **75847-73-3**, Enalapril 76420-72-9, Enalaprilat **76547-98-3**, Lisinopril 79902-63-9, Simvastatin 81093-37-0, Pravastatin 82768-85-2, Quinaprilat 82834-16-0, Perindopril 83435-66-9, Delapril 83647-97-6, Spirapril **85441-61-8**, Quinapril **86541-75-5**, Benazepril 87269-97-4, Ramiprilat **87333-19-5**, Ramipril 87679-37-6, Trandolapril **87679-71-8**, Trandolaprilat 88768-40-5, Cilazapril **89371-37-9**, Imidapril 93957-54-1, Fluvastatin 95399-71-6, Fosinoprilat **98048-97-6**, Fosinopril **103775-10-6**, Moexipril **111223-26-8**, Ceranapril 111902-57-9, Temocapril 124750-99-8, Losartan potassium 133040-01-4, Eprosartan 137862-53-4, Valsartan 138402-11-6, Irbesartan 139481-59-7, Candesartan 142695-08-7, MDL 100240 144701-48-4, Telmisartan 145040-37-5, Candesartan cilexetil 145733-36-4, Tasosartan 167305-00-2, Omapatrilat
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(renin-angiotensin system inhibitor for prevention of cardiovascular event, and use with other agents)

L38 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:302523 HCAPLUS

DOCUMENT NUMBER: 132:317822

TITLE: Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to **angiotensin-converting enzyme inhibitors**

AUTHOR(S): Granger, Christopher B.; Ertl, Georg; Kuch, Jerzy; Maggioni, Aldo P.; McMurray, John; Rouleau, Jean-Lucien; Stevenson, Lynn Warner; Swedberg, Karl; Young, James; **Yusuf, Salim**; Califf, Robert M.; Bart, Bradley A.; Held, Peter; Michelson, Eric L.; Sellers, Mary Ann; Ohlin, Gunilla; Sparapani, Rodney; Pfeffer, Marc A.

CORPORATE SOURCE: Duke Clinical Research Institute, Durham, NC, 27710, USA

SOURCE: American Heart Journal (2000), 139(4), 609-617
CODEN: AHJOA2; ISSN: 0002-8703

PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Many patients with congestive heart failure do not receive the benefits of angiotensin-converting enzyme (ACE) inhibitors because of intolerance. We sought to det. the tolerability of an angiotensin II receptor blocker, candesartan cilexetil, among patients considered intolerant of ACE inhibitors. Methods: Patients with CHF, left ventricular ejection fraction less than 35%, and history of discontinuing an ACE inhibitor because of intolerance underwent double-blind randomization in a 2:1 ratio to receive candesartan (n = 179) or a placebo (n = 91). The initial dosage of candesartan was 4 mg/d; the dosage was increased to 16 mg/d if the drug was tolerated. A history of intolerance of ACE inhibitor was attributed to cough (67% of patients), hypotension (15%), or renal dysfunction (11%). Results: The study drug was continued for 12 wk by 82.7% of patients who received candesartan vs. 86.8% of patients who received the placebo. This 4.1% greater discontinuation rate with active therapy was not significant; the 95% confidence interval ranged from 4.8% more discontinuation with placebo to 13% more with candesartan. Titrn. to the 16-mg target dose was possible for 69% of patients who received candesartan vs. 84% of those who received the placebo. Frequencies of death and morbidity were not significantly different between the candesartan and placebo groups (death 3.4% and 3.3%, worsening heart failure 8.4% and 13.2%, myocardial infarction 2.8% and 5.5%, all-cause hospitalization 12.8% and 18.7%, and death or hospitalization for heart failure 11.7% and 14.3%). Conclusions: Candesartan was well tolerated by this population. The effect of candesartan on major clin. end points, including death, remains to be detd.
CC 1-8 (Pharmacology)
ST candesartan cilexetil congestive heart failure; **angiotensin II antagonist** candesartan cilexetil
IT Angiotensin receptor **antagonists**
(**angiotensin II**; candesartan cilexetil treatment of humans with congestive heart failure and intolerance to **ACE inhibitors**)
IT Heart, disease
(failure; candesartan cilexetil treatment of humans with congestive heart failure and intolerance to **ACE inhibitors**)
IT 145040-37-5, Candesartan cilexetil
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(candesartan cilexetil treatment of humans with congestive heart failure and intolerance to **ACE inhibitors**)
IT **9015-82-1**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**inhibitors**; candesartan cilexetil treatment of humans with congestive heart failure and intolerance to **ACE inhibitors**)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:621212 HCAPLUS
DOCUMENT NUMBER: 131:223252
TITLE: Comparison of candesartan, enalapril, and their combination in congestive heart failure. randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. the RESOLVD pilot

study investigators
AUTHOR(S): McKelvie, R. S.; **Yusuf, S.**; Pericak, D.; Avezum, A.; Burns, R. J.; Probstfield, J.; Tsuyuki, R. T.; White, M.; Rouleau, J.; Latini, R.; Maggioni, A.; Young, J.; Pogue, J.
CORPORATE SOURCE: Writing Committee, McMaster University, Hamilton Health Sciences Corporation-General Division, Hamilton, ON, Can.
SOURCE: Circulation (1999), 100(10), 1056-1064
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background-We investigated the effects of candesartan (an angiotensin II antagonist) alone, enalapril alone, and their combination on exercise tolerance, ventricular function, quality of life (QOL), neurohormone levels, and tolerability in congestive heart failure (CHF). Methods and Results-Seven hundred sixty-eight patients in New York Heart Assocn. functional class (NYHA-FC) II to IV with ejection fraction (EF) <0.40 and a 6-min walk distance (6MWD) <500 m received either candesartan (4, 8, or 16 mg), candesartan (4 or 8 mg) plus 20 mg of enalapril, or 20 mg of enalapril for 43 wk. There were no differences among groups with regard to 6MWD, NYHA-FC, or QOL. EF increased (P=NS) more with candesartan-plus-enalapril therapy (0.025.+-.0.004) than with candesartan alone (0.015.+-.0.004) or enalapril alone(0.015.+-.0.005). End-diastolic (EDV) and end-systolic (ESV) vols. increased less with combination therapy (EDV 8.+-.4 mL; ESV 1.+-.4 mL; P<0.01) than with candesartan alone (EDV 27.+-.4 mL; ESV 18.+-.3 mL) or enalapril alone (EDV 23.+-.7 mL; ESV 14.+-.6 mL). Blood pressure decreased with combination therapy (6.+-.1/4.+-.1 mm Hg) compared with candesartan or enalapril alone (P<0.05). Aldosterone decreased (P<0.05) with combination therapy (23.2.+-.5.3 pg/mL) at 17 but not 43 wk compared with candesartan (0.7.+-.7.8 pg/mL) or enalapril (-0.8.+-.11.3 pg/mL). Brain natriuretic peptide decreased with combination therapy (5.8.+-.2.7 pmol/L; P<0.01) compared with candesartan (4.4.+-.3.8 pmol/L) and enalapril alone (4.0.+-.5.0 pmol/L). Conclusions-Candesartan alone was as effective, safe, and tolerable as enalapril. The combination of candesartan and enalapril was more beneficial for preventing left ventricular remodeling than either candesartan or enalapril alone.

CC 1-8 (Pharmacology)
Section cross-reference(s): 2

IT Angiotensin receptor **antagonists**
(**angiotensin II**; comparison of candesartan, enalapril, and combination in congestive heart failure in humans)

IT **75847-73-3**, Enalapril 139481-59-7, Candesartan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of candesartan, enalapril, and combination in congestive heart failure in humans)

IT **9015-82-1**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; comparison of candesartan, enalapril, and combination in congestive heart failure in humans)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:65345 HCAPLUS
DOCUMENT NUMBER: 128:188479

TITLE: Combination neurohormonal blockade with **ACE inhibitors, angiotensin II antagonists** and beta-blockers in patients with congestive heart failure: design of the randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study

AUTHOR(S): Tsuyuki, Ross T.; **Yusuf, Salim**; Rouleau, Jean L.; Maggioni, Aldo P.; Mckelvie, Robert S.; Wiecek, Elizabeth M.; Wang, Yong; Pogue, Janice; Teo, Koon K.; White, Michel; Avezum, Alvaro; Latini, Roberto; Held, Peter; Lindgren, Eva; Probstfield, Jeffrey

CORPORATE SOURCE: Can.

SOURCE: Canadian Journal of Cardiology (1997), 13(12), 1166-1174
CODEN: CJCAEX; ISSN: 0828-282X

PUBLISHER: Pulsus Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study is a trial of combination neurohormonal blockade using an angiotensin II antagonist (candesartan), an angiotensin-converting enzyme inhibitor (enalapril) and a beta-blocker (metoprolol) in patients with congestive heart failure (CHF). Primary objectives of stage I are to det. the efficacy (via the 6 min walk test) and safety of candesartan alone, and in combination with enalapril, vs. enalapril alone. Secondary objectives are to det. the effect of the above combinations on neurohormones, ventricular function, quality of life and symptoms. Stage II objectives are similar, evaluating the effect of the addn. of metoprolol or placebo to the above medication(s). The design consists of a randomized, two-stage trial consisting of a three-way comparison (stage I), followed by a 3.times.2 partial factorial design (stage II). Sixty our-patient clinics in five countries. Patients included have symptoms of CHF (New York Heart Assocn. functional classes II to IV), ejection fraction less than 40% and 6 min walk distance of 500 m or less. In stage I, 770 patients are randomized to receive candesartan alone, enalapril alone, or candesartan plus enalapril. After five months (end of stage I), patients are assessed for eligibility to be randomized in stage II. Those who are not candidates for randomization to beta-blocker or placebo are followed on their stage I medications until the end of the study. In stage II, patients are randomized to receive metoprolol or placebo for a further six months in addn. to their stage I medications. Endpoints are measured at baseline, end of stage I (week 20) and end of stage II (week 46). The study has recently completed follow-up in both stages. The findings from this study will be used to design a large scale mortality study that will help further define the role of neurohormonal blockade in patients with CHF.

CC 1-8 (Pharmacology)

ST **ACE inhibitor angiotensin II antagonist**; beta blocker congestive heart failure

IT Angiotensin receptor **antagonists**
(**angiotensin II; ACE inhibitor, angiotensin II antagonist** and beta-blocker treatment of humans with congestive heart failure)

IT Heart, disease
(failure; **ACE inhibitor, angiotensin II antagonist** and beta-blocker treatment of humans with congestive heart failure)

IT Adrenoceptor **antagonists**
(.beta.-; **ACE inhibitor, angiotensin**

II antagonist and beta-blocker treatment of humans with congestive heart failure)

IT 51384-51-1, Metoprolol **75847-73-3**, Enalapril 139481-59-7, Candesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ACE inhibitor, angiotensin II antagonist** and beta-blocker treatment of humans with congestive heart failure)

IT **9015-82-1**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; ACE inhibitor, angiotensin II antagonist** and beta-blocker treatment of humans with congestive heart failure)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> fil wpids
FILE 'WPIDS' ENTERED AT 11:56:44 ON 14 JUL 2003
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     (FILE 'WPIDS' ENTERED AT 11:36:43 ON 14 JUL 2003)
                DEL HIS Y
                E ANDERSON C/AU
L1           644 S E3-31
                E YUSUF S/AU
L2             7 S E3-4
L3            13 S E6-9
                E SLEIGHT P/AU
                E HILBRICH L/AU
L4           651 S L1-L2
L5          1336 S ANGIOTENSIN II OR ANG II
L6           897 S L5 (S) ANTAGON?
L7          2627 S ACE OR ANGIOTENSIN (2W) CONVERT? ENZYME#
L8          1902 S L7 (S) INHIBIT?
L9             2 S SARTAN#
L10          580 S BENAZEPRIL OR CAPTOPRIL OR CERONAPRIL OR ENALAPRIL OR FOSINOP
L11          187 S QUINAPRIL OR RAMIPRIL OR TRANDOLAPRIL OR PERINDOPRIL
L12          646 S L10 OR L11
L13         2210 S L12 OR L8
L14          898 S L6 OR L9
L15          143 S L13 AND L14
L16            0 S L9 AND L13
L17        16632 S DEMENTIA OR ALZHEIMER? OR SENIL? OR PARANOI? OR AMENTIA
L18           23 S L17 AND L15
L19         1116 S CO ADMINIST?
L20            1 S L19 AND L18
L21            4 S L4 AND L8 AND L13

     FILE 'WPIDS' ENTERED AT 11:56:23 ON 14 JUL 2003

     FILE 'WPIDS' ENTERED AT 11:56:44 ON 14 JUL 2003

=> d .wp l18 1-23;d .wp l20;d .wp l21 1-4

L18  ANSWER 1 OF 23  WPIDS (C) 2003 THOMSON DERWENT
```

AN 2003-457421 [43] WPIDS
DNC C2003-121782
TI Composition, useful for treating, e.g. vascular and neurodegenerative disorders such as **Alzheimer**'s Disease or atherosclerosis, comprises liver X receptor alpha agonist.
DC B01 B05
IN LIAO, S; SONG, C
PA (UYCH-N) UNIV CHICAGO
CYC 102
PI WO 2003039480 A2 20030515 (200343)* EN 23p
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2003039480 A2 WO 2002-US35900 20021108
PRAI US 2001-348020P 20011108
AB WO2003039480 A UPAB: 20030707
NOVELTY - A pharmaceutical composition comprises liver X receptor alpha agonist.

DETAILED DESCRIPTION - A pharmaceutical composition comprises a liver X receptor alpha agonist of formula (I), its salt, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug or derivatives.

R1-R7, R11, R12, R15, R16, R20 = alkyl (optionally substituted by NH, -N(alkyl)-, O, S, SO, SO2, O-SO2, SO2-O, SO3-O, CO, CO2, O-CO, CO-NR' or NR'-CO), H, halo, (halo)alkyl, OH, amino, carboxyl, oxo or sulfonic acid;

R8-R10, R13, R14 = H, halo, (halo)alkyl, hydroxyalkyl, alkoxy, OH or amino;

n = 0-2;

A = alkylene, alkenylene or alkynylene;

X, Y, Z = (halo)alkyl, OR', SR', NR'R'', N(OR')R'' or N(SR')R'';

X+Y = =O, =S or =NR1;

R', R'' = H or (halo)alkyl.

ACTIVITY - Vasotropic; Antiarteriosclerotic; Nootropic; Neuroprotective.

MECHANISM OF ACTION - Liver X receptor alpha agonist; **Angiotensin converting enzyme inhibitor**; **Angiotensin II** receptor **antagonist**; Dopamine receptor agonist/**antagonist**.

The liver X receptor agonistic activity of 3- alpha ,6- alpha ,24-trihydroxy-5- beta -24,24-di(trifluoromethyl)-cholestane (A) was evaluated in a gene transaction assay as described in Song, C. et. al., Steroids, 2000, 65, 423-427. Human embryonic kidney 293 cells were seeded into a 48-well culture plate at 105 cells/well in a Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum. After incubation for 24 hours, the cells were transfected by the calcium phosphate coprecipitation method with pGL3/UREluc reporter gene (250 ng) containing three copies of AGGTCAagccAGGTCA fused to nucleotide of the human c-fos promoter (-56 - +109) in front of the firefly luciferase gene in the plasmid basic pGL3, pSG5/hRXR- alpha (40 ng), pSG5/rUR or CMX/hliver X receptor alpha (each 40 ng), pSG5/hGrip1 (10 ng), CMV/R-luc (0.4 ng) and carrier DNA (250 ng). After incubation for another 12-24 hours, the cells were washed with phosphate buffer saline and then refed with DMEM supplemented with 4% delipidated fetal bovine serum. (A) showed ED50 value of 20 nM.

USE - The composition is used for activating liver X receptor alpha and treating a disease or disorder such as vascular disorder and neurodegenerative disorder related to a high blood serum cholesterol, e.g.

atherosclerosis, **senile** cognitive impairment, **dementia** and **Alzheimer**'s disease (claimed).

ADVANTAGE - (I) does not show significant toxic side effects.

Dwg.0/0

TECH UPTX: 20030707

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The composition additionally comprises an excipient (preferably binder, disintegrant, filler, surfactant, solubilizer, stabilizer, lubricant, wetting agent, diluent, anti-adherent, glidant or carrier).

L18 ANSWER 2 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-268133 [26] WPIDS
DNC C2003-069982
TI Use of **angiotensin converting enzyme** **inhibitor** to treat conditions associated with excess angiotensin enzyme activity e.g. muscular, renal, pulmonary and neuropsychiatric diseases .
DC B01 B02
IN MOSKOWITZ, D W
PA (GENO-N) GENOMED LLC
CYC 100
PI WO 2003013434 A2 20030220 (200326)* EN 22p
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2003040509 A1 20030227 (200330)
ADT WO 2003013434 A2 WO 2002-US25001 20020806; US 2003040509 A1 Provisional US 2001-310064P 20010806, Provisional US 2002-347013P 20020111, Provisional US 2002-347905P 20020115, Provisional US 2002-350563P 20020124, Provisional US 2002-352072P 20020128, Provisional US 2002-352074P 20020128, Provisional US 2002-352484P 20020130, Provisional US 2002-378467P 20020508, Provisional US 2002-379796P 20020513, Provisional US 2002-380741P 20020516, US 2002-213330 20020806
PRAI US 2002-380741P 20020516; US 2001-310064P 20010806; US 2002-347013P 20020111; US 2002-347905P 20020115; US 2002-350563P 20020124; US 2002-352072P 20020128; US 2002-352074P 20020128; US 2002-352484P 20020130; US 2002-378467P 20020508; US 2002-379796P 20020513; US 2002-213330 20020806
AB WO2003013434 A UPAB: 20030428
NOVELTY - Treatment of diseases associated with excess angiotensin enzyme activity comprises administration of an **angiotensin converting enzyme** (**ACE**) **inhibitor** to **inhibit** tissue **ACE**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) Tablet formulation for treating disorders associated with the **ACE** D/D genotype comprises an amount of **ACE** **inhibitor** to **inhibit** greater than 95% of tissue **ACE** or a dosage delivering greater than 80 mg/day of an **ACE inhibitor**; and

(2) Method of determining if a disease can be treated with **ACE inhibitors** involves calculating the odds ratio of association between a disease and the **ACE** D/D genotype and determining if the odds ratio is greater than 1.0.

ACTIVITY - Anorectic; Antigout; Antiasthmatic; Antiulcer; Antidiabetic; Virucide; Hepatotropic; Antiinflammatory; Osteopathic; Antiarthritic; Antirheumatic; Cytostatic; Antismoking; Nootropic;

Neuroleptic; Antidepressant; Ophthalmological; Dermatological; Antiallergic; Cerebroprotective; Analgesic; Anti-HIV; Nephrotropic; Litholytic; Thrombolytic; Antiarteriosclerotic; Respiratory; Antilipemic; Endocrine; Antipsoriatic; Gastrointestinal; Antimigraine; Antiparkinsonian; Tranquilizer; Tuberculostatic; Hypotensive; Neuroprotective; Antidote; Antiaddictive.

A 74 year old white male and a 73 year old black male who were heavy smokers with hypertension, severe atherosclerotic coronary artery disease and a serum creatinine level of 3 were treated with **Quinapril** (2 mg/kg/day) in addition to vigorous blood pressure and lipid lowering. Revascularization was delayed for 4 to 5 years in both cases.

MECHANISM OF ACTION - **Angiotensin Converting Enzyme Inhibitor.**

USE - Treatment of diseases associated with excess angiotensin enzyme activity including end-stage renal disease with hypertension, end-stage renal disease with non-insulin dependent diabetes mellitus, end stage renal disease due to focal segmental glomerulosclerosis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, kidney stones, immunoglobulin A glomerulonephritis, obstructive uropathy, acquired renal cystic disease of end-stage renal disease, cigarette abuse, asthma, pulmonary hypertension, pulmonary embolism, left ventricular hypertrophy, atherosclerotic peripheral vascular disease, deep vein thrombosis, chronic obstructive pulmonary disease, emphysema, obesity, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, retinopathy or neuropathy due to non-insulin dependent diabetes mellitus, scleroderma, lupus, gout, hypothyroidism, tertiary hyperparathyroidism in end-stage renal disease, the need for frequent de-clotting of vascular access in end-stage renal disease patients, Paget's disease, osteoporosis, allergy to penicillin or sulfa, allergic sinusitis or rhinitis, pelvic inflammatory diseases, prevention of hip fractures, eczema, psoriasis, basal cell skin cancer, osteoarthritis, degenerative disc disease, rheumatoid arthritis, gastro-esophageal reflux disease, gallstones, peptic ulcer disease, hiatal hernia, diverticulosis, gastritis, pancreatitis, ascites, alcoholic hepatitis, cirrhosis, cholecystitis, diverticulitis, irritable bowel syndrome, inflammatory bowel disease, inguinal hernia, solid tumors, leukemia, lymphomas, stroke, seizures, **Alzheimer**'s disease, **dementia**, headaches, migraine, parkinsonism, multi-infarct **dementia**, bipolar affective disorder, schizophrenia, depression, anxiety, drug abuse, glaucoma, cataracts, presbycusis, viral hepatitis A or B, tuberculosis or HIV infection or complications of HIV infection e.g. HIV-associated nephropathy or AIDS (all claimed).

Dwg.0/0

TECH UPTX: 20030428

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: Greater than 95% of the tissue **ACE** is **inhibited**. The **ACE inhibitor** is used in combination with a second active agent such as aldosterone or a compound to increase aldosterone levels, an anti-hypertensive, fludrocortisone acetate (for patients with plasma potassium ion concentration of above 4.5 mEq/l), an **angiotensin II** receptor **antagonist** or a diuretic. The method can be used to treat non-human animals.

Preferred Formulation: The tablet formulation has a controlled or sustained release carrier.

L18 ANSWER 3 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-040721 [03] WPIDS
DNC C2003-009704
TI New dextrorotatory atropisomer of N-((2'-(((4,5-dimethyl-3-isoxazolyl)amino)sulfonyl)-4-(2-oxazolyl)(1,1'-biphenyl)-2-yl)methyl)-

N,3,3-trimethylbutanamide useful in the treatment of e.g. hypertension.
DC B03
IN HUGHES, D E; SEIDENBERG, B C
PA (HUGH-I) HUGHES D E; (SEID-I) SEIDENBERG B C; (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 100
PI WO 2002083130 A1 20021024 (200303)* EN 24p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003040534 A1 20030227 (200318)
ADT WO 2002083130 A1 WO 2002-US11992 20020412; US 2003040534 A1 Provisional US 2001-284080P 20010416, US 2002-121520 20020412
PRAI US 2001-284080P 20010416; US 2002-121520 20020412
AB WO 200283130 A UPAB: 20030113
NOVELTY - (+)N-((2'-(((4,5-dimethyl-3-isoxazolyl)amino)sulfonyl-4-(2-oxazolyl)(1,1'-biphenyl)-2-yl)methyl)-N,3,3-trimethylbutanamide (I) or its lithium, sodium or potassium salt or a salt formed with an organic amine base is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the composition comprising (I) and a vehicle or carrier.

ACTIVITY - Vasotropic; Cytostatic; Hypotensive; Antimigraine; Antiarteriosclerotic; Cardiant; Cerebroprotective; Hemostatic; Antiasthmatic; Antidiabetic; Neuroprotective; Tranquilizer; Vulnerary; Analgesic; Antimigraine; Antiulcer; Antiinflammatory; Hepatotropic; Dermatological; Nephrotropic; Ophthalmological; Anticonvulsant; Antipsoriatic; Antiarthritic; Antirheumatic; Osteopathic; Nootropic.

MECHANISM OF ACTION - Endothelin antagonist; Endothelin A receptor binder. CHO-K1 cells expressing the human endothelin A receptor were cultured. The binding assay was performed in assay buffer (125 micro l) (50 mM tris, pH 7.4, including 1% BSA and 2 micro M phosphoramidon) maintained at 4 deg. C and 25 micro l of either ET-1 (control) or (+)N-((2'-(((4,5-dimethyl-3-isoxazolyl)amino)sulfonyl)-4-(2-oxazolyl)(1,1'-biphenyl)-2-yl)methyl)-N,3,3-trimethylbutanamide (test) (99% pure). The reaction was initiated with the addition of 25 micro l of 0.25 nM test. Incubation was carried out with gentle orbital shaking at 4 deg. C, reaching equilibrium at 4 hours. The reaction was terminated by aspiration of the reaction buffer and two subsequent washes with room temperature PBS (Mg++, Ca++ free). The cells were dissociated by the addition of 0.5N NaOH (100 micro l) followed by incubation for 40 minutes. Samples were then transferred from the 96 well format into tubes for counting in a Cobra gamma counter. The results showed that the IC50 for test/control was 0.01/0.1.

USE - For the treatment of endothelin related disorders, hypertension, pulmonary hypertension, primary pulmonary hypertension, benign prostatic hypertrophy, migraine, renal, glomerular or mesangial cell disorders, endotoxemia, ischemia, atherosclerosis, restenosis, subarachnoid hemorrhage, congestive heart failure, asthma, intermittent claudication, diabetic neuropathy and cancer (claimed). Also for treatment of conditions associated with increased ET levels (e.g. dialysis, trauma or surgery) and of all endothelin-dependent disorders; for alleviation of pain associated cancer; prevention and/or reduction of end-organ damage associated the cell-proliferative effects of endothelin; for treatment of cardiac, renal and cerebral ischemia and reperfusion (such as that occurring following cardiopulmonary bypass surgery), coronary and cerebral vasospasm; as an adjuncts to thrombolytic therapy; in therapy for

myocardial infarction; for peripheral vascular disease (e.g. Raynaud's disease and Takayashu's disease); treatment of cardiac hypertrophy (e.g. hypertrophic cardiomyopathy); treatment of primary pulmonary hypertension (e.g. plexogenic, embolic) in adults and in the newborn, radiation and chemotherapeutic injury or other trauma; treatment of central nervous system vascular disorders (e.g. stroke and subarachnoid hemorrhage); treatment of central nervous system behavioral disorders; treatment of gastrointestinal diseases (e.g. ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer, inflammatory bowel disease or ischemic bowel disease); treatment of gall bladder or bile duct-based diseases such as cholangitis; treatment of pancreatitis; regulation of cell growth; treatment of benign prostatic hypertrophy; restenosis following angioplasty or following any procedure including transplantation and stenting; therapy for congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling and dysfunction; treatment of hepatotoxicity and sudden death; treatment of sickle cell disease; treatment of the deleterious consequences of ET-producing tumors such as hypertension resulting from hemangiopericytoma; treatment of early and advanced liver disease and injury including attendant complications (e.g. hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder; treatment of hepatorenal syndrome; treatment of immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia; treatment of fibrosis associated with renal dysfunction and hepatotoxicity; in therapy for metabolic and neurological disorders; cancer; insulin-dependent and non insulin-dependent diabetes mellitus; neuropathy; retinopathy; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; chronic inflammatory diseases such as arthritis, rheumatoid arthritis, osteoarthritis, sarcoidosis and eczematous dermatitis (all types of dermatitis); treatment of disorders involving bronchoconstriction and disorders of chronic or acute pulmonary inflammation such as chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS); treatment of sexual dysfunction in both men (erectile dysfunction) and women by improving blood flow to the genitalia; treatment of **dementia**, including **Alzheimer's dementia, senile dementia** and vascular **dementia**.

ADVANTAGE - The (+) dextrorotatory atropisomer demonstrates remarkably higher potency than either the (-) levorotatory or the racemate.

Dwg.0/0

TECH UPTX: 20030113

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general preparation given.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition additionally comprises at least one therapeutic agent (e.g. **angiotensin** (**II**) (AII) receptor **antagonist**, renin **inhibitor**, **angiotensin converting enzyme** (**ACE**) **inhibitor**, vasopepsidase **inhibitor** (preferably omapatrilat or gemopatrilat), antiplatelet agent (preferably clopidigrel, ticlopidine, CS-747 or aspirin), diuretic or cardiac glycoside.

L18 ANSWER 4 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-682675 [73] WPIDS
DNC C2002-192538
TI Treatment of patient to alleviate neurological disorders e.g. **Alzheimer's** disease, Parkinson's disease, **senile dementia** involves altering defective endothelium involves

administration of autologous blood cells.
DC B04 B05 D16
IN BOLTON, A E; MANDEL, A
PA (VASO-N) VASOGEN IRELAND LTD
CYC 100
PI WO 2002060461 A1 20020808 (200273)* EN 35p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
CA 2333494 A1 20020801 (200273) EN
ADT WO 2002060461 A1 WO 2002-CA127 20020201; CA 2333494 A1 CA 2001-2333494 20010201
PRAI CA 2001-2333494 20010201
AB WO 200260461 A UPAB: 20021113
NOVELTY - Treatment of a patient to alleviate a neurological disorder involves altering the defective endothelium towards normalization of its function by administration of autologous blood cells that have been extracorporeally stressed by subjection to appropriate amounts of oxidative stress.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for a method of treating a patient to alleviate a neurological disorder involves:

(i) diagnosing patients to determine the presence of defective endothelial functions in brain blood vessels;

(ii) selecting patients diagnosed with defective blood vessel, endothelial function; and

(iii) administering autologous blood.

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Immunosuppressive; Hypotensive; Antilipemic.

MECHANISM OF ACTION - None given.

USE - In the preparation of medicament for treating neuro-degenerative disorder (claimed) such as **Alzheimer**'s disease, Parkinson's disease, **senile dementia**; and also autoimmune disorders, hypertension, and hyperlipidemia.

Four patients, human females ranging in age 15 - 84 years and all suffering from an endothelium deficiency-related condition were subjected to a course of treatment of autologous stressed blood cells. Each treatment administered to the patient involved removing a aliquot (10 ml) of the patient's blood into an apparatus, heating the sample to 42.5 deg. C and exposing it to UV radiation at wavelength 253.7 nm. Upon reaching the required temperature (42.5 deg. C), a gaseous mixture of medical grade oxygen with an ozone content (12.5 micro g/ml), at flow rate of about 60 ml/minute was bubbled through the sample for 3 minutes. After the ex vivo treatment of the blood sample had been completed, the sample was injected into the respective patient via the gluteal muscle. Each patient underwent a course of 10 such treatments over a period of 2 - 4 weeks, the individual treatments being spaced apart by about 1 - 3 days. The patient reported a very significant alleviation of her Raynaud's symptoms, after completion of the course of treatments, indicative of an improvement in endothelial function.

ADVANTAGE - The method improves the performance of endothelial function at the blood brain barrier towards restoration of normal endothelial function.

Dwg.0/5
TECH UPTX: 20021113
TECHNOLOGY FOCUS - BIOLOGY - Preferred Method: The cells have additionally

been stress by simultaneously extracorporeally subjected to UV light or an elevated temperature. The oxidative stressor is exposed to a mixture of medical grade oxygen and ozone gas (300 microg/ml). The oxygen/ozone gas mixture is bubbled through a suspension of blood cells at a rate of 0.01 - 2 l/minutes. The suspension of blood cells is whole blood (0.1 - 100 ml). The blood cells are additionally subjected to elevated temperature of 40 - 50degreesC simultaneously with the subjection to oxidative stress.
ACE inhibitor (a), **angiotensin II**
receptor **antagonist** (b), **inhibitor** of the enzyme HMG
CoA reductase (c) or dihydropyridine-type calcium channel blocker drug (d) is administered in combination with the medicament.
Preferred Components (a) is alacepril, **benazepril**, **captopril**, **ceronapril**, cilazapril, delapril, **enalapril**, enalaprilat, **fosinopril**, **imidapril**, **lisinopril**, moveltopril, **perindopril**, **quinapril**, **ramipril**, spirapril, temocapril or **trandolapril**. (b) is candesartan, eprosartan, irbesartan, losartan or valsartan. (c) is atorvastatin, fluvastatin, lovastatin, simvastatin, pravastatin or cerivastatin. (d) is amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine or nitrendipine.

L18 ANSWER 5 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-443832 [47] WPIDS
DNC C2002-126239
TI Fibrinogen lowering agent used for treating e.g. hypercholesterolemia, thrombosis and central nervous system disorders comprises **angiotensin II antagonist**.
DC B02
IN HIRAKATA, M; IMURA, Y
PA (TAKE) TAKEDA CHEM IND LTD
CYC 97
PI WO 2002015935 A1 20020228 (200247)* JA 55p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001080135 A 20020304 (200247)
JP 2002138054 A 20020514 (200247) 21p
EP 1312379 A1 20030521 (200334) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002015935 A1 WO 2001-JP7239 20010824; AU 2001080135 A AU 2001-80135 20010824; JP 2002138054 A JP 2001-254391 20010824; EP 1312379 A1 EP 2001-958449 20010824, WO 2001-JP7239 20010824
FDT AU 2001080135 A Based on WO 200215935; EP 1312379 A1 Based on WO 200215935
PRAI JP 2000-260881 20000825
AB WO 200215935 A UPAB: 20020725
NOVELTY - Fibrinogen lowering agent comprises an **angiotensin II antagonist** (excluding 'ilebesaletan') or its prodrugs and/or salts.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for agents for treating and preventing hypercholesterolemia, hyperfibrogenemia or kidney disorders associated with hyperfibrogenemia which comprises a renin-angiotensin system inhibitor.
ACTIVITY - Antilipemic; Nephrotropic; Cardiant; Antianginal; Vasotropic; Cerebroprotective; Neuroprotective; Thrombolytic;

Antidiabetic; Ophthalmological; Antiinflammatory; Hemostatic; Antiarteriosclerotic; Respiratory; Mydriatic; Immunomodulator; Nootropic; Tranquilizer; Cytostatic; Antiarthritic; Antirheumatic; Antiallergic; Dermatological; Immunosuppressive; Hepatotropic; Antibacterial; Vulnerary; Gastrointestinal; Osteopathic.

MECHANISM OF ACTION - Fibrinogen **antagonist**; **Angiotensin-II antagonist**; Acetylcholine esterase inhibitor; Renin inhibitor; Chymase inhibitor; Aldosterone **antagonist**; Cholesterol **antagonist**.

Candesartan cilexetil (Ia) administered to SHC rats at 1 mg/kg/day gave blood fibrinogen levels of 354.0 mg/dl compared to 496.4 mg/dl for a control.

USE - Used for treating and preventing e.g. hypercholesterolemia, hyperfibrogenemia or kidney disorders associated with hyperfibrogenemia (claimed), fatty heart, chronic cardiac insufficiency, angina pectoris, cardiac infarction, transient ischemic attack, cerebral apoplexy, cerebral edema, nerve damage due to cerebral thrombosis, diabetes, diabetic complications (e.g. diabetic retinopathy or neuropathy), nephritis, glomerular sclerosis, renal insufficiency, thrombocytopenia, arteriosclerosis, thrombosis (e.g. deep vein thrombosis or pulmonary thrombosis), reocclusion, multiple organ failure, subarachnoid hemorrhage, syndrome X, hyperlipemia, cachexia, CNS disorders (e.g. head trauma or multiple sclerosis), **dementia**, memory disorders, anxiety, acute inflammatory disorders, cancer, rheumatoid arthritis, allergic rhinitis, anaphylaxis, systemic lupus erythematosus, chronic hepatitis, liver cirrhosis, Kawasaki's disease, toxemia, toxic shock, keloids, nerve degeneration disorders, allergic disorders, digestive system disorders, osteopathies, respiratory system disorders, toxemia and dermatological disorders.

Dwg.0/0

TECH UPTX: 20020725

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Agent: **Angiotensin II antagonist** is a nonpeptide, contains an oxygen atom and/or has an ether bond or carbonyl group and is preferably a benzimidazole compound of formula (I).

Renin-angiotensin system **inhibitor** is an **angiotensin-II antagonist**, an **angiotensin converting enzyme inhibitor**, renin **inhibitor**, chymase **inhibitor** or aldosterone **antagonist**.

R1, R2 = anionic group or group which may be converted into an anionic group;
X = absent or spacer containing 1 or 2 atoms in the chain;
n = 1 or 2;
R3 = optionally substituted hydrocarbyl optionally attached via a heteroatom.
The benzene ring of benzimidazole is optionally substituted.

L18 ANSWER 6 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-405017 [43] WPIDS
DNC C2002-113753
TI Treatment of e.g. **Alzheimer**'s disease comprises external application of pulses to fluid channels in patients' body.
DC B04 B05 D16
IN INMAN, D M; SACKNER, M A
PA (NONI-N) NON-INVASIVE MONITORING SYSTEMS INC
CYC 96
PI WO 2002026194 A2 20020404 (200243)* EN 207p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2002012996 A 20020408 (200252)

US 2002103454 A1 20020801 (200253)

ADT WO 2002026194 A2 WO 2001-US30789 20010928; AU 2002012996 A AU 2002-12996 20010928; US 2002103454 A1 Provisional US 2000-236221P 20000928, US 2001-967422 20010928

FDT AU 2002012996 A Based on WO 200226194

PRAI US 2000-236221P 20000928; US 2001-967422 20010928

AB WO 200226194 A UPAB: 20020709

NOVELTY - Treating (I) e.g. **Alzheimer**'s disease comprising the external application of pulses to the fluid channels in the patients' body, is new.

DETAILED DESCRIPTION - Treatment of e.g. **Alzheimer**'s disease comprises:

(a) periodically accelerating at least one part of the body using a periodic acceleration device, externally and non-invasively apply a pulse to the fluid channels (A1) over the body's own pulse (A2); and

(b) stimulating endothelial release of beneficial mediators and suppressing non-beneficial mediators. The pulses are not synchronized with (A2).

An INDEPENDENT CLAIM is included for diagnosing (II) a subject involving steps (a) and (b) and testing the physiological response of the subject either during or immediately after step (b) using the device.

ACTIVITY - Nootropic; Neuroprotective; Cerebroprotective; Hemostatic; Antiparkinson; Anticonvulsant; Antiinflammatory; Vasotropic; Antibacterial; Immunosuppressive; Cardiant; Thrombolytic; Osteopathic; Antianginal; Antiarteriosclerotic; Hypotensive; Opthalmological; Antidiabetic; Anorectic; Tranquilizer; Vulnerary; Antidepressant; Analgesic; Auditory; Antirheumatic; Antiarthritic; Anti-HIV; Cytostatic; Antitumor.

MECHANISM OF ACTION - Inhibitor; Promoter; Stimulator.

USE - The method is useful for treating depression, chronic fatigue syndrome, panic, anxiety, schizophrenia, conversion and somatoform pain disorder, alcohol abuse and dependence, **Alzheimer**'s disease, acute brain injury, chronic neurogenerative disease, inflammation, heart disorders, impaired lymphatic drainage, for promoting bone growth where mediator release is deficient, for providing cerebrospinal fluid drainage, vasodilation and increased blood flow, chronic heart failure, acute myocardial infarction, vasopathic angina, coronary atherosclerosis and asymptomatic coronary artery disease, diastolic dysfunction, systemic, portal, obesity related and pulmonary hypertension, Raynauld's phenomenon, proliferative retinopathy, insulin resistance syndrome, wide-angle glaucoma, macular degeneration, angina pectoris, restenosis, vasospastic angina, for preparing the myocardium for redo coronary bypass graft surgery and graft failure, type-2 diabetes mellitus, preconditioning the heart to minimize reperfusion injury, myocardial ischemia, renal failure complicated by arterial stiffness, chronic atrial fibrillation, ischemic stroke, subarachnoid hemorrhage, for a neonatal patient with neonatal pulmonary hypertension caused by genetic deficiency of endothelial nitric oxide synthase (eNOS), bronchopulmonary dysplasia, pulmonary embolism, venous stasis, endothelial dysfunction, dysmenorrhea, preeclampsia, preterm cervical dilitation, traumatic brain injury, pain management, sleep deprivation, sudden deafness and Menier's disease, lymphatic damage, adult respiratory distress syndrome and meconium aspiration syndrome, osteoporosis, bone fractures, fibromyalgia, wounds, bed sores, tendon damage, acute gastric injury, HIV-1 infection, erectile dysfunction, cancer, prostate cancer with an overexpression of endothelin-1 and for the

improvement of memory and cognitive function. Method (II) is useful for diagnosing atherosclerosis, hypercholesterolemia, insulin resistance syndrome, arterial smooth muscle dysfunction, microvascular cerebrovascular disorders and normal pressure glaucoma, diabetes and chronic heart failure (all claimed).

ADVANTAGE - The method stimulates the endothelial release of beneficial mediator and suppresses non-beneficial mediators so the pulses do not encroach on the patient pulse wave. Advantages also include e.g. endothelial release of nitric oxide, prostacyclin and tissue plasminogen activator and suppression of endothelin-1, tissue plasminogen inhibitor and antigen helps prevent graft rejection. For vasopathic angina (I) upregulates coronary vascular eNOS to release nitric oxide thus diminishing the frequency and intensity of coronary spasm episodes. During treatment of hepatic veno-occlusive disease (I) upregulates endothelial storage and release of tissue plasmingen activator and suppresses tissue plasminogen inhibitor. The externally added pulses improve memory and cognitive function.

Dwg.0/0

TECH UPTX: 20020709

TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred Method: Step (a) involves providing external intermittent compression of at least one of the legs, thighs and buttocks and at least one of air and liquid filled bladders attached to reservoirs and pumps around at least one of legs, thighs and buttocks. Exercising on a treadmill within a lower body negative pressure chamber to maintain bone, neuromuscular and cardiovascular fitness on long space flights in microgravitational fields. In (II), the periodic acceleration device controls the frequency and intensity of the pulses. Step (b) involves analyzing a dicrotic notch on a diastolic limb of an arterial pulse. Downward descent of the dicrotic notch is a function of nitric oxide released and absent or diminished descent of dicrotic notch relative to response of normally functioning endothelium is caused by endothelial dysfunction; and computing a b/a ratio. The b/a ratio is the height of the dicrotic notch upward inflection point from its location on arterial pulse to the end-diastolic level (2) divided by total pulse amplitude height (1). The dicrotic notch is determined using non-invasive sensors, which are placed on at least one of thumbs, fingers, toes, neck and skin or over at least one radical, brachial, carotid, subclavian and femoral arteries. Step (b) involves computing dose response curves by plotting frequency, amplitude and peak acceleration of pulses against a b/a ratio and comparing the computed dose response curve to control curves. The control curves comprise one of the subject after applying a nitric oxide donor drug that relaxes vascular smooth muscle independent of endothelial participation and dose response curves of a normal population. (II) involves displaying the arterial pulse on a display and removing pulses from the display involving using triggered electro-cardiographic R-wave ensemble-averaging and to display on averaged vascular pulse, or triggered ensemble-averaging of input from at least one of linear displacement, velocity or acceleration sensors mounted on the device into (A1) or subject to obtain an averaged externally added pulse output and subtracting the averaged externally added pulses output from an averaged vascular pulse output while accounting for differences of phase and gain characteristics between the two outputs. (II) involves displaying at least one of an averaged vascular pulse, an averaged mathematical first derivative from the average vascular pulse along with an averaged electrocardiographic waveform for timing purposes. Step (b) involves analyzing an Augmentation Index of the arterial pulse wave velocity which is computed by dividing the distance between two remote arterial sites by the difference in time of onset of two remote arterial waveforms. The Augmentation Index is a ratio of the amplitude of presence wave between its initial systolic shoulder to the

peak divided by the pulse amplitude. An increase in a baseline of the Augmentation Index or in the arterial pulse wave velocity relative to a response of normally functioning endothelium is caused by endothelial dysfunction. Step (b) involves analyzing central venous pressure where a decrease in pressure is caused by normal endothelial function and little or no change occurs in the presence of endothelial dysfunction, or involves analyzing E wave deceleration time where the time is computed from the mathematical derivative of the left ventricular volume curve. Since the endothelial dysfunction of the heart corresponds to diastolic dysfunction, the E wave deceleration time during the addition of external pulses is substantially unchanged relative to a response of normally functioning endothelium. Step (b) involves analyzing blood flow of the subject, utilizing biochemical markers to test the response of the subject, utilizing a blood coagulation test or analyzing baroceptor sensitivity as a plot of RR intervals of an electrocardiogram against a rate of arterial distension from a thumb or finger inductive plethysmograph. A lesser increase in blood flow relative to a response of normally functioning endothelium is caused by endothelial dysfunction; the extent of change in levels of biochemical marker and a decrease or increase in fibrinogen degradation products.

Preferred Components: (A) comprises running or jumping by the subject. When the subject is a baby, (A) comprises a carriage, which is pushed back and forth by a caregiver. The biochemical marker is one of urinary serum, blood serum, plasma nitrite/nitrate or nitric oxide. A blood flow measuring device comprises venous occlusion plethysmography with a limb inductive plethysmograph, mercury on rubber or silastic strain gauges and droppler ultrasound imaging. A device for measuring the left ventricular volume curve is a thoracic inductive plethysmograph (thoracocardiograph) and a device for measuring the central venous pressure is a neck inductive plethysmograph. The non-invasive sensors comprise a digital inductive plethysmograph or at least one of oscillometric plethysmographs, piezoelectric sensors, mercury in rubber or silastic strain gauges, photoelectric plethysmographs, pulse oximeter, impedance plethysmograph, capacitance condenser microphone and electric pneumoplethysmographs.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: (I) involves controlling the frequency and intensity of the pulses. In (a), the pulses are added repeatedly using (A), over (A2) to at least one of vascular circulation, heart, lymphatics, interstitial spaces and bone interstices. Even during periods when pulses are not imparted, bioavailability of the beneficial mediators is greater than in the pretreatment period. Step (a) involves modulating vascular endothelial growth factor (VEGF), provides a periodic acceleration for pulsing with a frequency of 1 - 6 Hz and a periodic acceleration up to about +/-0.6 g and the added pulses are visible over the patient's own pulse waveform on a vascular pulse waveform trace display. Step (a) involves providing a receprocating movement platform for shifting the patient in headwards-footwards direction using a horizontal platform drawn by a controllable fly wheel-motor mechanism; providing a device for fixing the patient to the movement platform with a vertical foot-board along with attachments to immobilize at least one of the feet and legs such that movement which is transmitted by the platform is conveyed to the patient without substantial out-of-phase body movement relative to platform movement; providing a seat within a wheel chair driven by an adjustable frequency movement device (B1), and a device for shifting the patient's legs up and down while the patient is seated. Step (a) involves providing a device to utilize high frequency oscillatory ventilation with bias flow and added apparatus dead space which adds pulses to the body's fluid channels through the lungs. When (I) is for a prospective donor of at least one organ for transplantation the patient is given phosphodiesterase **inhibitors** and the organ is preserved.

When the beneficial mediator is nitric oxide, (I) involves testing a

response of the patient by analyzing a dicrotic notch present on a diastolic limb of an arterial pulse, analysing the Augmentation Index of the patient's arterial pulse, analyzing arterial pulse wave velocity, analyzing central venous pressure, analyzing E wave deceleration time, analyzing peripheral blood flow, utilizing biochemicals markers and utilizing blood coagulation test or testing a response of the patient by utilizing the biochemical makers, which are released as products or metabolites from endothelial tissue. (I) involves administering a drug and providing pulses, limiting drug administration, minimizing uncounted side effects and obtaining unique beneficial effects. Step (b) provides at least one of the effects (B3) additive and synergistic vasodilator, antiplatelet aggregation and antileukocyte adhesion actions. When the drug is a statin, the combination of drug administration and pulses provides bone building in addition to (B3). To prevent the inflammatory consequences of hemorrhagic shock and the drug is both a macrophage or smooth muscle inducible NOS (iNOS) **inhibitor** and a scavenger of peroxinitrate, step (ii) in combination with drug administration provides a useful adjunct to appropriate electrolyte and fluid balance. For septic shock the macrophage or smooth muscle inducible NOS (iNOS) **inhibitor** provides lower pulmonary vascular resistance. For impaired lymphatic drainage measurement of volume changes using a limb plethysmograph is used to test the efficacy of (I). For acute myocardial infarction and restenosis platelet Glycoprotein GPIIb - IIIa complex **inhibitor** is administered. For portal hypertension iNOS **inhibitors** are administered. For deep venous thrombosis heparin, a heparin-like product, a recombinant tissue plasminogen activator and a streptokinase to provide one of additive and synergistic action are administered. For **Alzheimer**'s disease, Parkinson's, multiple sclerosis or traumatic brain injury at least one of iNOS and neuronal nitric oxide synthase (nNOS) **inhibitors** are administered. For traumatic brain injury a narcotic is administered. For rheumatoid, juvenile and osteoarthritis iNOS **inhibitors** are administered. For wounds light and laser therapy provide one of additive and synergistic actions. For HIV-1 infection cisplatin is administered.
Preferred Device: (B1) comprises a cam adjustable for vertical displacement and a rotary motor mechanism and a flywheel drive motor assembly. (B2) comprises an adjustable frequency, cam adjustable for vertical displacement and rotary motor mechanism.
Preferred Components: The NOS **inhibitor** is one of macrophage or smooth muscle inducible NOS (iNOS) and neuronal NOS (nNOS) **inhibitor**. The iNOS **inhibitor** is 1400 W, aminoguanidine, radical, L-NIL and interferon-beta. The nNOS **inhibitor** is ARR17338 and ARL17477. The scavanger of peroxynitrate is mercaptoethylguanidine. The drug is at least one of L-Arginine, insulin, an **angiotensin converting enzyme** (**ACE**) **inhibitor**, an **angiotensin II** receptor blocker, Angiotensin-(1 - 7), aspirin, an iloprost, a beta blocker, a calcium **antagonist** (preferably pranidipin) that upregulate the activity of superoxide dismutase, statin, an estrogen, an atrial natriuretic peptide, an intravenous clot buster (preferably recombinant tPA), phosphodiesterase **inhibitor**-3, -4 or -5, a xanthin oxidase **inhibitor**, an endothelin receptor **antagonist**, SC52608 (a synthesized superoxidase dismutase mimic), a platelet aggregation **inhibitor** (preferably YC-1), furoxins or S-nitrosothiol derivative that releases nitric oxide slowly and a prostaglandin. For **Alzheimer**'s disease, the drug is a monamine oxidase-B **inhibitor**, L-deprenyl. For acute brain injury and chronic neurogenerative disease, the drug is NOS **inhibitor**.

L18 ANSWER 7 OF 23 WPIDS (C) 2003 THOMSON DERWENT

AN 2002-188332 [24] WPIDS
DNC C2002-058139
TI Use of rapamycin in treatment or inhibition of a cardiovascular, cerebral vascular and peripheral vascular disease e.g. atherosclerosis, in a mammal.
DC B02 C02
IN ADELMAN, S J; AZROLAN, N I; SEHGAL, S N
PA (AMHP) AMERICAN HOME PROD CORP; (AMHP) WYETH
CYC 97
PI WO 2001097809 A2 20011227 (200224)* EN 17p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
US 2002013335 A1 20020131 (200224)
AU 2001068446 A 20020102 (200230)
NO 2002006008 A 20021213 (200318)
EP 1292302 A2 20030319 (200322) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003010710 A 20030205 (200338)
ADT WO 2001097809 A2 WO 2001-US19179 20010614; US 2002013335 A1 Provisional US 2000-212117P 20000616, US 2001-880295 20010613; AU 2001068446 A AU 2001-68446 20010614; NO 2002006008 A WO 2001-US19179 20010614, NO 2002-6008 20021213; EP 1292302 A2 EP 2001-946387 20010614, WO 2001-US19179 20010614; KR 2003010710 A KR 2002-717036 20021213
FDT AU 2001068446 A Based on WO 200197809; EP 1292302 A2 Based on WO 200197809
PRAI US 2000-212117P 20000616; US 2001-880295 20010613
AB WO 200197809 A UPAB: 20020416
NOVELTY - Treating or inhibiting cardiovascular, cerebral vascular and peripheral vascular disease in mammal involves administering an effective amount of rapamycin.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a product comprising rapamycin in combination with:

(a) at least one agent selected from an **ACE inhibitor**,

(b) an **angiotensin-II** receptor **antagonist**,

(c) a fibric acid derivative,

(d) a HMG Co-A reductase inhibitor,

(e) a beta adrenergic blocking agent,

(f) a calcium channel blocker,

(g) an antioxidant,

(h) an anticoagulant, or

(i) an agent useful in hormone replacement therapy containing an estrogen.

ACTIVITY - Cardiant; Cerebroprotective; Immunosuppressive; Antiarteriosclerotic; Nootropic.

MECHANISM OF ACTION - Lipid concentration modulator. Male EKO mice, 4 - 6 weeks of age, were allowed ad lib food and water and randomized by body weight into 5 groups containing 12 - 15 mice per group. The mice were fed with Purina Rodent Chow for the first week. The diet was then switched to a casein-based western diet for 2 - 13 weeks and in the similar period the mice were also dose every two days with 0, 1, 2, 4 or 8 mg/kg of rapamycin using Tween-80 (2% surfactant) and 1% carboxymethyl cellulose as a vehicle. The administration of only the vehicle was considered as a control. At the end of the study the animals were euthanized, the plasma samples were obtained and the concentration of total cholesterol,

triglycerides, VLDL-cholesterol (C1), LDL-(C1), HDL-(C1) was determined, along with the atherosclerotic lesions, on the aortas. The concentration of triglycerides (mg/dl), total cholesterol (mg/dl), VLDL-C (mg/dl), LDL-C (mg/dl), HDL-C (mg/dl) and aortic atherosclerosis (% lesion involvement) for 1 mg/kg rapamycin/control were: 132 plus or minus 16/140 plus or minus 13, 1434 plus or minus 35/1186 plus or minus 47, 903 plus or minus 34/807 plus or minus 48, 508 plus or minus 18/371 plus or minus 13, 23 plus or minus 6/7 plus or minus 3, and 21.6 plus or minus 3:1/39.5 plus or minus /2.6 respectively. Thus, the treatment with rapamycin significantly increased (p less than 0.01) levels of HDL-C and LDL-C, while not affecting level of triglycerides, total cholesterol and VLDL cholesterol, compared with control EKO mice.

USE - For treating or inhibiting cardiovascular, cerebral vascular and peripheral vascular disease e.g. coronary artery disease, arteriosclerosis, atherosclerosis, non-atheromatous arteriosclerosis, vascular wall damage from cellular events leading toward immune mediated vascular damage, stroke, multiinfarct **dementia** in a mammal (claimed).

Dwg.0/0

TECH UPTX: 20020416

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Drugs: Rapamycin is an ester (preferably 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methyl propionic acid), ether (preferably 42-ether with O-(2-hydroxy)ethyl rapamycin), an oxime, a hydrazone, or a hydroxylamine of rapamycin.

L18 ANSWER 8 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-179658 [23] WPIDS
DNC C2002-055798
TI Transdermal therapeutic system, containing highly dispersed silicon dioxide in matrix or adhesive layer to promote drug permeation through the skin.
DC B07 P32 P34
IN KLOKKERS, K; KRAMER, K; WILHELM, M
PA (HEXA-N) HEXAL AG
CYC 96
PI WO 2002003969 A2 20020117 (200223)* DE 28p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
DE 10033853 A1 20020131 (200223)
AU 2001072535 A 20020121 (200234)
EP 1301179 A2 20030416 (200328) DE
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002003969 A2 WO 2001-EP8070 20010712; DE 10033853 A1 DE 2000-10033853 20000712; AU 2001072535 A AU 2001-72535 20010712; EP 1301179 A2 EP 2001-951670 20010712, WO 2001-EP8070 20010712
FDT AU 2001072535 A Based on WO 200203969; EP 1301179 A2 Based on WO 200203969
PRAI DE 2000-10033853 20000712
AB WO 200203969 A UPAB: 20020411
NOVELTY - In a transdermal therapeutic system (TTS) comprising an impermeable backing layer, one or more matrix layers (at least one of which is self-adhesive) containing active agent(s) (A) and a removable backing layer, highly dispersed silicon dioxide (I) is contained in the matrix layer(s) to increase permeation through the skin.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for two alternative forms of the TTS, in which:

(a) the matrix layer(s) is/are coated with an adhesive layer (rather than being self-adhesive) and (I) is contained in the adhesive layer; or

(b) the matrix layer(s) is/are replaced by an (A)-containing reservoir layer provided with a semipermeable membrane and an adhesive layer, (I) being contained in the adhesive layer.

USE - The TTS is useful for the administration of a wide range of drugs and other biologically active agents, e.g. androgens, estrogens, gestagens, proton pump **inhibitors**, 5-HT1 **antagonists**, sympatholytics, sympathomimetics, anticholinergics, tranquilizers, anxiolytics, antiaddictive agents, analgesics, calcium **antagonists**, antiemetics, vasodilators, anticoagulants, anti-parkinsonian agents, anti-**dementia** agents, choline esterase **inhibitors**, **ACE inhibitors**, antihistamines, antiulcer agents, H2 receptor blockers, **angiotensin II antagonists**, neuroleptics, antidepressants, local anesthetics and/or hypolipemic agents.

ADVANTAGE - (I) is an effective permeation promoter which is readily availably, well tolerated by the skin, non-allergenic and compatible with many (A). The permeation of more than one (A) may be promoted simultaneously.

Dwg.0/0

TECH UPTX: 20020411

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (I) is homogeneously incorporated in the appropriate layer(s), preferably by swelling a mixture of adhesive matrix (or adhesive) and (I) in presence of a liquid medium then shaping the mixture to form the adhesive or matrix layer(s). (I) is contained in a sufficient amount to increase or adjust the permeation to a predetermined value, especially a maximum value, suitable for. In particular (I) forms 0.1-10 (preferably 2-5) wt. % of the appropriate layer(s). (I) is especially Aerosil (RTM) 200 and/or R972. The TTS may additionally include stabilizers, emulsifiers, thickeners, other permeation promoters and/or conventional membrane system or reservoir plaster auxiliaries.

L18 ANSWER 9 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-098049 [13] WPIDS
DNC C2002-030599
TI New pyridine containing compounds useful as 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor in the treatment of e.g. cholesterol-related diseases.
DC B02
IN CHEN, B; ROBL, J A; SUN, C
PA (CHEN-I) CHEN B; (ROBL-I) ROBL J A; (SUNC-I) SUN C; (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 97
PI WO 2001096347 A1 20011220 (200213)* EN 106p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002013334 A1 20020131 (200216)
AU 2001066858 A 20011224 (200227)
US 2002094977 A1 20020718 (200254)
NO 2002006012 A 20030203 (200322)
EP 1294728 A1 20030326 (200323) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
CZ 2002003930 A3 20030312 (200324)

ADT WO 2001096347 A1 WO 2001-US18864 20010612; US 2002013334 A1 Provisional US 2000-211595P 20000615, US 2001-875155 20010606; AU 2001066858 A AU 2001-66858 20010612; US 2002094977 A1 Provisional US 2000-211595P 20000615, CIP of US 2001-875155 20010606, US 2001-7407 20011204; NO 2002006012 A WO 2001-US18864 20010612, NO 2002-6012 20021213; EP 1294728 A1 EP 2001-944447 20010612, WO 2001-US18864 20010612; CZ 2002003930 A3 WO 2001-US18864 20010612, CZ 2002-3930 20010612

FDT AU 2001066858 A Based on WO 200196347; EP 1294728 A1 Based on WO 200196347; CZ 2002003930 A3 Based on WO 200196347

PRAI US 2000-211595P 20000615; US 2001-875155 20010606; US 2001-7407 20011204

AB WO 200196347 A UPAB: 20020226

NOVELTY - Pyridine-containing compounds (I) are new.

DETAILED DESCRIPTION - Pyridine-containing compounds of formula (I), their salts (where R3 is H), ester, prodrug ester and stereosisomer are new.

X = O, S, or NR7;

Z' = -CH(OH)-CH2-C(R8)(OH)-CH2-CO2R3 or a group of formula (i);

asterisk = attachment point;

n = 0 or 1;

R1 and R2 = alkyl, aryalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R3 and R8 = H or lower alkyl;

R4 = H, halo, CF3, hydroxy, alkyl, alkoxy, alkanoylamino, aroylamino, or cyano;

R7 = H, alkyl, aryl, alkanoyl, aroyl, or alkoxycarbonyl;

R9 and R10 = H or alkyl;

R9+R10 = 3 - 7 membered carbocyclic ring;

dashed line = cis or trans single or double bond.

INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical combination comprising (I) and at least one hypolipidemic agent (1), lipid-lowering agent (2), lipid agent (3), lipid modulating agent (4), at least one other type of therapeutic agent (5) including antidiabetic agent (6), anti-obesity agent (7), antihypertensive agent (8), platelet aggregation inhibitor (9), anti-**dementia** agent (10), anti-**Alzheimer**'s agent (11), antiosteoporosis agent (12), and/or hormone replacement therapeutic agent (13), other cardiovascular agent (14) including anti-anginal agent (15), anti-arrhythmic agent (16), anti-atherosclerosis agent (17), anti-inflammatory agent (18), anti-arthritis agent (19), anti-platelet agent (20), anti-heart failure agent (21)), anti-cancer agent (22), anti-infective agent (23), hormone replacement agent (24), growth hormone secretagogues (25), selective androgen receptor modulator (26), and/or immunomodulatory agent (27); and

(2) an intermediate of formula (II).

Q = -CO2T, CH2OH, -CH2-halide, -CH2-P(=O)(W)-W or a group of formula (ii);

T = alkyl; and

W = aryl, alkyl or alkoxy.

ACTIVITY - Antilipemic; Antiarteriosclerotic; Nootropic; Neuroprotective; Osteopathic; Cerebroprotective; Cardiant; Antiangial; Hypotensive; Antidiabetic; Anorectic; Cytostatic; Antiinflammatory; Litholytic; Hepatotropic; Anti-HIV; Antipsoriatic; Antiarrhythmic; Vasotropic; Anorectic.

MECHANISM OF ACTION - 3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor.

USE - (I) are used for inhibiting cholesterol biosynthesis or lowering blood serum cholesterol levels and/or modulating blood serum cholesterol levels, lowering low density lipoprotein (LDL) cholesterol and/or increasing high density lipoprotein (HDL) cholesterol, or treating

dyslipidemia, mixed dyslipidemia, LDL Pattern B, LDL Pattern A, hyperlipidemia, hypercholesterolemia, hypo alpha -lipoproteinemia, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, reducing levels of Lp(a); treating or preventing other cholesterol-related diseases; treating, preventing or reversing progression of atherosclerosis, **Alzheimer**'s disease, osteoporosis, osteopenia; reducing inflammatory markers, reducing C-reactive protein, or preventing or treating low grade vascular inflammation, stroke, **dementia**, coronary heart disease, primary and secondary prevention of myocardial infarction, stable and unstable angina, primary prevention of coronary events, secondary prevention of cardiovascular events, peripheral vascular disease, peripheral arterial disease, acute vascular syndromes, reducing the risk of undergoing myocardial revascularization procedure, microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, hypertension, Type I and 2 diabetes and related diseases, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial tumors, cancer induced asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gall stones, and HIV infection, drug-induced lipodystrophy, proliferative diseases such as psoriasis, improving coagulation homeostasis, reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, cerebrovascular diseases (all claimed). Dwg.0/0

TECH UPTX: 20020226

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The saturated derivative of (IB) (where a is CH2-CH2) is obtained by catalytic (Pd/C, Pt/C, Pd(OH)2) hydrogenation of (IA).

Preferred Compound: The compound is of formula (III) or its internal lactone, (IV), its alkali or alkaline earth metal salt, amino acid salt, or acid addition salt via the pyridine of the corresponding delta lactone, (V) or (VI) or their salts or internal lactones.

R'3 = H, an alkali or alkaline earth metal ion, an amino acid;
R5 and R6 = H, halo or alkyl;
R'2 = alkyl or cycloalkyl;
W' = -CH(CH3)2 or cyclopropyl.

The intermediate is of formula (VIII) - (XI).

G' = CO2R, -CH2-OH, -CH2-halide, or -CH2-P(W)2=O; and
dashed line = single or double bond.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (1) - (4) or (17) comprises at least one metalloprotease (MTP) **inhibitor**, 3-huydroxy-3-methylglutaryl-coenzyme-A (HMG CoA) reductase **inhibitor**, squalene synthetase **inhibitor**, fibric acid derivative, peroxisome proliferator activated receptors (PPAR)alpha agonist, PPAR dual alpha/gamma agonist, PPAR delta agonist, acyl coenzyme A;cholesterol acyl transferase (ACAT) **inhibitor**, lipoxygenase **inhibitor**, cholesterol absorption **inhibitor**, ileal Na+/bile acid cotransporter **inhibitor**, upregulator of low density lipoprotein (LDL) receptor activity, cholesteryl ester transfer protein **inhibitor**, bile acid sequestrant, or nicotinic acid and their derivatives, adenosine triphosphatase (ATP) citrate lyase **inhibitor**, phytoestrogen compound, an high density lipoprotein (HDL) upregulator, LDL catabolism promoter, antioxidant, phosphpolylipase (PLA)-2 **inhibitor**, antihomocysteine agent, HMG-CoA synthase **inhibitor**, lanosterol demethylase **inhibitor**, or sterol regulating element binding protein-I agent. (6) is at least one antidiabetic agent or antihyperglycemic agent including insulin

secretagogues or insulin sensitizer, which may include biguanide, sulfonyl urea, PTP (undefined)-1B **inhibitor**, aldose reductase **inhibitor**, glucosidase **inhibitor**, PPARgamma agonist, PPARalpha agonist, PPARdelta **antagonist** or agonist, aP2 **inhibitor**, PPAR alpha/gamma dual agonist, dipeptidyl peptidase IV (DP4) **inhibitor**, SGLT2 **inhibitor**, glycogen phosphorylase **inhibitor**, and/or meglitinides, insulin, and/or glucagon-like peptide-1 (GLP-1) or their mimetics (preferably metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A). (5) is a beta 3 adrenergic agonist, a lipase **inhibitor**, a serotonin (and dopamine) reuptake **inhibitor**, an aP2 **inhibitor**, a thyroid receptor beta drug, an anorectic agent, a PTP-1B **inhibitor**, a CCKA agonist, a neuropeptide Y **antagonist**, a melanocortin-4-receptor agonist, a PPAR modulator which is a PPARgamma **antagonist**, PPARalpha agonist, and/or PPARdelta **antagonist**, a leptin **inhibitor** such as a leptin receptor activator, a fatty acid oxidation upregulator or inducer. (4) is an MTP **inhibitor**, an HMG CoA reductase **inhibitor**, a squalene synthetase **inhibitor**, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase **inhibitor**, or an ACAT **inhibitor** (preferably pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, pitavastatin, rosuvastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin, and/or LY295427). (3) is a cholesteryl ester transfer protein **inhibitor**. (8) is an **ACE inhibitor** (preferably **captopril**, **fosinopril**, **enalapril**, **lisinopril**, **quinapril**, **benazepril**, fentiapril, **ramipril** or **moexipril**, especially **ramipril**), **angiotensin II** receptor **antagonist** (preferably irbesartan, losartan or valsartan), NEP (undefined) **inhibitor**, a NEP/**ACE inhibitor** (preferably omapatrilat, gemopatrilat, or CGS 30440, especially omapatrilat or gemopatrilat), a calcium channel blocker, a T-channel calcium **antagonist**, a a-adrenergic blocker, a diuretic, a a-adrenergic blocker, a dual action receptor **antagonist**, or a heart failure drug (preferably amlodipine besylate, prazosin HCI, verapamil, nifedipine, nadolol, propranolol, or clonidine HCI, carvediol, atenolol, hydrochlorothiazide, torasemide, furosemide, spironolactone or indapamide). (7) is orlistat, ATL962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol, P57 or CP-644673. (9) is aspirin, clopidogrel, ticlopidine, dipyridamole, ifetroban, abciximab, tirofiban, eptifibatide, or anagrelide (preferably aspirin and/or clopidogrel). (5) is (10) or (11) (preferably Cognex (RTM; tacrine HCl), Aricept (RTM; donepezil), gamma secretase inhibtor, a beta-secretase **inhibitor** and/or antihypertensive agent), (12) (preferably parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist), (13) (preferably a selective estrogen receptor modulator), a tyrosine kinase **inhibitor**, a selective androgen receptor modulator, (16) (preferably a beta-blocker, or a calcium channel blocker, or an a-adrenergic blocker), coenzyme Q sub. 10, an agent that upregulates type III endothelial cell nitric acid syntase, a chondroprotective compound (preferably polysulfated glycosaminoglycan, glucosamine, chondroitin sulfate, hyaluronic acid, pentosan polysulfate, doxycycline or minocycline), a cyclooxygenase (COX)-2 **inhibitor** (preferably Celebrex or Vioxx or a glycoprotein IIa/IIIb receptor **antagonist**

), a 5-HT reuptake **inhibitor**, (25), (17), (23), an immunosuppressant for use in transplantation, or an antineoplastic agent.

L18 ANSWER 10 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-098045 [13] WPIDS
DNC C2002-030595
TI New pyridine-containing compound for treating e.g. hyperlipedemia, hypercholesterolemia, **Alzheimer**'s disease, osteoporosis.
DC B05
IN CHEN, B; ROBL, J A; SUN, C
PA (CHEN-I) CHEN B; (ROBL-I) ROBL J A; (SUNC-I) SUN C; (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 97
PI WO 2001096311 A2 20011220 (200213)* EN 106p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002028826 A1 20020307 (200221)
AU 2001066860 A 20011224 (200227)
US 2002061901 A1 20020523 (200239)
NO 2002006011 A 20030212 (200321)
EP 1294696 A2 20030326 (200323) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
CZ 2002003931 A3 20030312 (200324)
KR 2003010720 A 20030205 (200338)
ADT WO 2001096311 A2 WO 2001-US18868 20010612; US 2002028826 A1 Provisional US 2000-211594P 20000615, US 2001-875218 20010606; AU 2001066860 A AU 2001-66860 20010612; US 2002061901 A1 Provisional US 2000-211594P 20000615, CIP of US 2001-875218 20010606, US 2001-8154 20011204; NO 2002006011 A WO 2001-US18868 20010612, NO 2002-6011 20021213; EP 1294696 A2 EP 2001-944449 20010612, WO 2001-US18868 20010612; CZ 2002003931 A3 WO 2001-US18868 20010612, CZ 2002-3931 20010612; KR 2003010720 A KR 2002-717087 20021214
FDT AU 2001066860 A Based on WO 200196311; EP 1294696 A2 Based on WO 200196311; CZ 2002003931 A3 Based on WO 200196311
PRAI US 2000-211594P 20000615; US 2001-875218 20010606; US 2001-8154 20011204
AB WO 200196311 A UPAB: 20020226
NOVELTY - Pyridine-containing compound is new.
DETAILED DESCRIPTION - Pyridine-containing compounds of formula (I), or their salts (when R3 is H), prodrug ester, or stereoisomer is new.
Z' = -CH(OH)-CH2-C(R7)(OH)-CH2-CO2R3 or a group of formula (i);
n = 0 or 1;
x = 0-4;
y = 0-4;
R1 and R2 = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;
R3 = H or lower alkyl;
R4 = h, halo, CF3, hydroxy, alkyl, alkoxy, alkanoylamino or cyano;
R7 = H or lower alkyl;
dashed line = single or double bond which may be cis or trans.
With the proviso that at lest one of x and y is other than 0.
Optionally at least one carbons of (CH2)x and/or at least one carbon of (CH2)y together with additional carbons forms 3 - 7 membered spirocyclic ring.
INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical combination comprising (I) and at least one hypolipidemic agent (1), lipid-lowering agent (2), lipid agent (3), lipid modulating agent (4), at least one other type of therapeutic agent (5) including antidiabetic agent (6), anti-obesity agent (7), antihypertensive agent (8), platelet aggregation inhibitor (9), anti-**dementia** agent (10), anti-**Alzheimer**'s agent (11), antiosteoporosis agent (12), and/or hormone replacement therapeutic agent (13), other cardiovascular agent (14) including anti-anginal agent (15), anti-arrhythmic agent (16), anti-atherosclerosis agent (17), anti-inflammatory agent (18), anti-arthritis agent (19), anti-platelet agent (20), anti-heart failure agent (21)), anti-cancer agent (22), anti-infective agent (23), hormone replacement agent (24), growth hormone secretagogues (25), selective androgen receptor modulator (26), and/or immunomodulatory agent (27); and

(2) an intermediate of formula (II);

(3) a compound of formula (V).

Q = -CO2T, CH2OH, -CH2-halO, -CH2-P(=O)(W)-W or a group of formula (ii);

asterisk = attachment point;

R3'' = H, alkali/alkaline earth metal ion, amino acid or internal lactone in the form of its sodium, calcium or arginine salt;

T = alkyl; and

W = aryl, alkyl or alkoxy.

ACTIVITY - Antilipemic; Antiarteriosclerotic; Nootropic; Neuroprotective; Osteopathic; Antiinflammatory; Cerebroprotective; Cardiant; Antianginal; Hypotensive; Anti-diabetic; Anti-tumor; Cytostatic; Antiulcer; Ophthalmological; Anti-HIV; Vasotropic; Anorectic; Gastrointestinal; Antiarrhythmic.

MECHANISM OF ACTION - Metalloprotease (MTP) inhibitor; 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitor; squalene synthetase inhibitor; fibric acid derivative; peroxisome proliferator activated receptors (PPAR) alpha agonist; PPAR dual alpha / gamma agonist; PPAR delta agonist; acyl coenzyme A;cholesterol acyl transferase (ACAT) inhibitor; lipoxygenase inhibitor; cholesterol absorption inhibitor; ileal Na+/bile acid cotransporter inhibitor; upregulator of low density lipoprotein (LDL) receptor activity; cholesteryl ester transfer protein inhibitor; PTP-1B inhibitor; CCKA (undefined) agonist; neuropeptide Y antagonist,

USE - (I) is used for inhibiting cholesterol biosynthesis, lowering blood serum cholesterol levels and/or modulating blood serum cholesterol levels, lowering low density lipoprotein (LDL) cholesterol and/or increasing ADL (undefined) cholesterol, treating dyslipidemia, mixed dyslipidemia, LDL Pattern B, LDL Pattern A, hyperlipidemia, hypercholesterolemia, hypo alpha -lipoproteinemia, hyperlipoproteinemia, hypertriglyceridemia and other aberrations of apolipoprotein B metabolism, reducing levels of Lp(a), other cholesterol-related diseases, progression of atherosclerosis, **Alzheimer**'s disease, osteoporosis, osteopenia, inflammatory markers, C-reactive protein, preventing or treating low grade vascular inflammation, stroke, **dementia**, coronary heart disease, stable and unstable angina, peripheral vascular disease, peripheral arterial disease, acute vascular syndromes, the risk of undergoing myocardial revascularization procedures, microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, hypertension, Type I diabetes, Type 2 diabetes, and related diseases, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, LDL Pattern B, LDL Pattern A, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial tumors, cancer induced asthenia (fatigue), irritable bowel syndrome,

Crohn's disease, gastric ulceritis, and gallstones, and HIV infection, drug-induced lipodystrophy, and proliferative diseases, improving coagulation homeostasis, reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, and primary and secondary prevention of myocardial infarction, primary prevention of coronary events, or secondary prevention of cardiovascular events. Also for treating cholesterol related diseases, diabetes and related diseases, cardiovascular diseases and cerebrovascular diseases.

Dwg.0/0

TECH UPTX: 20020226

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The saturated derivative of (IB) (where a is CH2-CH2) is obtained by catalytic (Pd/C, Pt/C, Pd(OH)2) hydrogenation of (IA).

Preferred Compounds: The compound is of formula (III) or its alkali metal salt, alkaline earth metal salt, amino acid salt or an acid addition salt via the pyridine of the corresponding delta lactone; formula (IV), (V) or (VI) or their salt or internal lactone in the form of calcium salt, sodium salt or arginine salt; or formula (VII) or its internal lactone in the form of its sodium salt, calcium salt or arginine salt.

R2' = alkyl or cycloalkyl;

R3' = H, alkali metal, alkaline earth metal or amino acid salt;

R5 and R6 = H, halo or alkyl.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (1) - (4) or (17) comprises at least one metalloprotease (MTP) **inhibitor**, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase **inhibitor**, squalene synthetase **inhibitor**, fibric acid derivative, peroxisome proliferator activated receptors (PPAR)alpha agonist, PPAR dual alpha/gamma agonist, PPAR delta agonist, acyl coenzyme A;cholesterol acyl transferase (ACAT) **inhibitor**, lipoxygenase **inhibitor**, cholesterol absorption **inhibitor**, ileal Na+/bile acid cotransporter **inhibitor**, upregulator of low density lipoprotein (LDL) receptor activity, cholesteryl ester transfer protein **inhibitor**, bile acid sequestrant, or nicotinic acid and their derivatives, adenine triphosphatase (ATP) citrate lyase **inhibitor**, phytoestrogen compound, an high density lipoprotein (HDL) upregulator, LDL catabolism promoter, antioxidant, phosphopolylipase (PLA)-2 **inhibitor**, antihomocysteine agent, HMG-CoA synthase **inhibitor**, lanosterol demethylase **inhibitor**, or sterol regulating element binding protein-I agent. (6) is at least one antidiabetic agent or antihyperglycemic agent including insulin secretagogues or insulin sensitizer, which may include biguanide, sulfonyl urea, PTP-1B **inhibitor**, aldose reductase **inhibitor**, glucosidase **inhibitor**, PPARgamma agonist, PPARalpha agonist, PPARdelta **antagonist** or agonist, aP2 **inhibitor**, PPAR alpha/gamma dual agonist, dipeptidyl peptidase IV (DP4) **inhibitor**, SGLT2 **inhibitor**, glycogen phosphorylase **inhibitor**, and/or meglitinides, insulin, and/or glucagon-like peptide-1 (GLP-1) or their mimetics (preferably metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A). (5) is a beta 3 adrenergic agonist, a lipase **inhibitor**, a serotonin (and dopamine) reuptake **inhibitor**, an aP2 **inhibitor**, a thyroid receptor beta drug, an anorectic agent, a PTP-1B **inhibitor**, a CCKA (undefined) agonist, a neuropeptide Y **antagonist**, a melanocortin-4-receptor agonist, a PPAR modulator which is a PPARgamma **antagonist**, PPARalpha agonist, and/or PPARdelta **antagonist**, a leptin **inhibitor**

such as a leptin receptor activator, a fatty acid oxidation upregulator or inducer. (4) is an MTP **inhibitor**, an HMG CoA reductase **inhibitor**, a squalene synthetase **inhibitor**, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase **inhibitor**, or an ACAT **inhibitor** (preferably pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, pitavastatin, rosuvastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin, and/or LY295427). (3) is a cholesteryl ester transfer protein **inhibitor**. (8) is an **ACE inhibitor** (preferably **captopril**, **fosinopril**, **enalapril**, **lisinopril**, **quinapril**, **benazepril**, fentiapril, **ramipril** or **moexipril**, especially **ramipril**), **angiotensin II** receptor **antagonist** (preferably irbesartan, losartan or valsartan), NEP **inhibitor**, a NEP/**ACE inhibitor** (preferably omapatrilat, gemopatrilat, or CGS 30440, especially omapatrilat or gemopatrilat), a calcium channel blocker, a T-channel calcium **antagonist**, a a-adrenergic blocker, a diuretic, a a-adrenergic blocker, a dual action receptor **antagonist**, or a heart failure drug (preferably amlodipine besylate, prazosin HCI, verapamil, nifedipine, nadolol, propranolol, or clonidine HCI, carvediol, atenolol, hydrochlorothiazide, torasemide, furosemide, spironolactone or indapamide). (7) is orlistat, ATL962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol, P57 or CP-644673. (9) is aspirin, clopidogrel, ticlopidine, dipyridamole, ifetroban, abciximab, tirofiban, eptifibatide, or anagrelide (preferably aspirin and/or clopidogrel). (5) is (10) or (11) (preferably Cognex (RTM; tacrine HCl), Aricept (RTM; donepezil), gamma secretase inhibtor, a beta-secretase **inhibitor** and/or antihypertensive agent), (12) (preferably parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist), (13) (preferably a selective estrogen receptor modulator), a tyrosine kinase **inhibitor**, a selective androgen receptor modulator, (16) (preferably a beta-blocker, or a calcium channel blocker, or an a-adrenergic blocker), coenzyme Q sub. 10, an agent that upregulates type III endothelial cell nitric acid syntase, a chondroprotective compound (preferably polysulfated glycosaminoglycan, glucosamine, chondroitin sulfate, hyaluronic acid, pentosan polysulfate, doxycycline or minocycline), a cyclooxygenase (COX)-2 **inhibitor** (preferably Celebrex or Vioxx or a glycoprotein IIa/IIIb receptor **antagonist**), a 5-HT reuptake **inhibitor**, (25), (17), (23), an immunosuppressant for use in transplantation, or an antineoplastic agent.

L18 ANSWER 11 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-482984 [52] WPIDS
CR 2000-170974 [15]
DNC C2001-144714
TI New biphenyl sulfonamides, useful as angiotensin endothelin receptor antagonists and for treatment of e.g. hypertension, atherosclerosis, asthma and ischemia.
DC B05
IN GU, Z; MACOR, J E; MURUGESAN, N; TELLEW, J E
PA (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 93
PI WO 2001044239 A2 20010621 (200152)* EN 286p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR

LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK
SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001020926 A 20010625 (200162)
EP 1237888 A2 20020911 (200267) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
ADT WO 2001044239 A2 WO 2000-US33730 20001213; AU 2001020926 A AU 2001-20926
20001213; EP 1237888 A2 EP 2000-984282 20001213, WO 2000-US33730 20001213
FDT AU 2001020926 A Based on WO 200144239; EP 1237888 A2 Based on WO 200144239
PRAI US 2000-643640 20000822; US 1999-464037 19991215; US 2000-481197
20000111; US 2000-513779 20000225; US 2000-604322 20000626
AB WO 200144239 A UPAB: 20021022
NOVELTY - Biphenyl sulfonamides (I), and their enantiomers, diasteremers, salts and metabolites, are new.

DETAILED DESCRIPTION - Biphenyl sulfonamide compounds of formula (I), and their enantiomers, diasteremers, salts and metabolites, are new.

R1 = a group of formulae (a) - (o);

R2 = T or aryloxy, provided that when R1 is a group of formula (b), that R2 is not H, halo, (halo)alkyl, alkoxy, hydroxyalkyl, nitro, -(CH2)wNR19R20 or -NHSO2R22;

T = H, halo, CHO, (halo)alkyl, alkenyl, alkynyl, (halo)alkoxyalkyl, (cycloalkyl)alkyl, alkoxyalkoxy, cyano, hydroxy(alkyl), nitro, -CH(OR13)(OR14) or -(CH2)wY

R3 = heteroaryl;

R4, R5 = (hydroxy)alkyl, (hydroxy-substituted)cycloalkyl or (hydroxy-substituted)alkoxyalkyl; or

R4 and R5 together = cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl or tetrahydropyranyl (all optionally substituted with one or more OH);

R6 = (hydroxy)(halo)alkyl, (hydroxy-substituted)(cycloalkyl)alkyl, aralkyl, (hydroxy-substituted)alkoxy(alkyl) or -NR16R17;

R7 = -(CH2)w-CO2R15, -(CH2)w-(C=O)NR16R17, -(CH2)w-NR15(C=O)NR16R17, -(CH2)w-CH2OH or -(CH2)w-(C=O)R15, or tetrazolyl, oxadiazolyl or triazolyl (each optionally substituted with H, alkyl, OH or halo);

R8, R9, R9a, R10, R12 = H, halo, (hydroxy)alkyl, (cycloalkyl)(alkyl), (hetero)aryl, arylalkyl, alkylthioalkyl, alkoxy(alkyl); or

R11, R11a = H, alkoxy or together form a carbonyl;

R13, R14 = alkyl or together form a 5- or 6-membered ring;

R15, R16, R17 = H, (hydroxy)alkyl, (cycloalkyl)(alkyl), alkoxyalkyl, aralkyl, heterocycloalkyl, (hetero)aryl or -(CH2)wQ; or

R16 and R17 together = 4-6 membered heterocyclic ring;

n = 1 or 2;

w = 0, 1 or 2;

Y = heteroaryl, -COOH, -COOR18, -CONR19R20, -NR19-OR20, -NR21(C=O)R22, -NR21(C=O)NR19R20, -N(R19)-(alk)-NR21(C=O)R22, -NR21(C=O)OR18, -NR21SO2R22, -SO2R22, or a group of formulae (q), (r) or (s);

R18 - R22 = H, (halo)alkyl, alkoxyalkyl, cycloalkyl, alkenyl, alkynyl, (hetero)aryl or aralkyl; or

R19 and R20 together = 4-7 membered cycloalkyl ring;

R23, R24 = H, (cyclo)alkyl or together form a 3-7 membered ring;

Z = O, -N(R25)- or -C(R26)(R27)-;

x = 2,3 or 4;

R25, R26, R27 = H, (cyclo)alkyl or R26 and R27 together form a 3-7 membered cycloalkyl ring; and

R101 - R104 = T in which all (hetero)aryl rings are optionally substituted by H, halo, cyano, (hydroxy)alkyl, alkoxy, nitro or trifluoromethyl.

Provided that when R1 is a group of formula (a), (I) is not a compound of formula (II).

INDEPENDENT CLAIMS are also included for:

(1) a compound of formula (I) in which R3 = isoxazol-5-yl or isoxazol-3-yl (optionally substituted with 2 of alkyl or halogen, and R1 is any group such that the resulting compound demonstrates affinity (IC50) for both the AT1 receptor and ETA receptor of less than 5 mM at both receptors

(2) a pharmaceutical composition comprising (I), at least one **ACE inhibitor** (such as captotril, zofenopril, **fosinopril**, ceranapril, alacepril, **enalapril**, delapril, pentopril, **quinapril**, **ramipril**, or **lisinopril**), vasopepsidase **inhibitor** (such as omapatrilat or gemopatrilat), HMG CoA reductase **inhibitor** (such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 or ZD-4522), anti-platelet agent (such as clopidigrel, ticlopidine, CS-747 or aspirin), anti-diabetic agent (such as biguanides or biguanide/glyburide combinations), beta-adrenergic agent (such as carvedilol or metoprolol) or minerocorticoid receptor antagonist (such as spironolactone or eplerenone).

ACTIVITY - Antiarthritic; nootropic; neuroprotective; antianginal; antiarrhythmic; antiarteriosclerotic; antiinflammatory; analgesic; cytostatic; cardiant; cerebroprotective; hepatotropic; dermatological; ophthalmological; antidiabetic; antidiarrheic; anticonvulsant; vasotropic; litholytic; hemostatic; hypotensive; antimigraine; osteopathic; antipsoriatic; antiulcer.

MECHANISM OF ACTION - Endothelin receptor antagonist; angiotensin II receptor antagonist. Tests were carried out but no results are given.

USE - (I) are useful in the treatment of disorders related to renal, glomerular and mesangial cell function. For treatment of disorders related to paracrine and endocrine function. For treatment of endotoxemia or endotoxin shock or hemorrhagic shock. For alleviating pain associated with prostate and bone cancer. For preventing end-organ damage associated with the cell-proliferative effects of endothelin. For treatment of hypoxic and ischemic diseases (such as cardiac, renal and cerebral ischemia and reperfusion). As antiarrhythmic, antianginal, antifibrillatory, antiasthmatic, antiarteriosclerotic, and antidiarrheal agents. As adjuncts to thrombolytic therapy. For treatment of myocardial infarction, peripheral vascular disease (e.g. Raynaud's disease), cardiac hypertrophy, primary pulmonary hypertension, trauma, central nervous system vascular disorders (such as migraine, stroke and hemorrhage), central nervous system behavioural disorders, gastrointestinal diseases (such as Crohn's disease, ulcers and inflammatory bowel disease), pancreatitis and gall bladder disorders. For regulation of cell growth. For treatment of restenosis following transplantation. For therapy of congestive heart failure including inhibition of fibrosis. For treatment of sickle cell disease, liver disease, deleterious consequences of ET-producing tumors, spastic diseases of the urinary tract and bladder, hepatorenal syndrome, immunological diseases (including vasculitis) fibrosis associated with renal dysfunction, metabolic and neurological disorders, cancer, insulin-retinopathy, diabetes mellitus, neuropathy, retinopathy, epilepsy, bone remodelling, psoriasis, and chronic inflammatory diseases (such as arthritis, rheumatoid arthritis, osteoarthritis, sarcoidosis and eczematous dermatitis). For treatment of disorders involving broncoconstriction. For treatment of sexual dysfunction, Alzheimer's, senile dementia and vascular dementia.

Dwg.0/0

TECH UPTX: 20010914

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) can be prepared by:

(1) reacting a sulfonyl-substituted phenyl bromide with an phenyl boronic acid (or ester) to form a biphenyl sulfonyl compound;

(2) converting the biphenyl sulfonyl compound into a biphenyl sulfonyl chloride; and
(3) reacting the biphenyl sulfonyl chloride compound with an aryl amine.

L18 ANSWER 12 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-335775 [35] WPIDS
DNN N2001-242411 DNC C2001-103702
TI Treating a disease in a subject characterized by increased levels of c-Jun homodimers or heterodimers, phosphorylated c-Jun, and/or Jun kinase, involves administering a compound effective to ameliorate the symptoms.
DC B02 B04 D16 S03
IN PETERSON, T C
PA (UYDA-N) UNIV DALHOUSIE
CYC 94
PI WO 2001032156 A2 20010510 (200135)* EN 34p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001012944 A 20010514 (200149)
US 6294350 B1 20010925 (200158)
ADT WO 2001032156 A2 WO 2000-IB1731 20001102; AU 2001012944 A AU 2001-12944 20001102; US 6294350 B1 CIP of US 1997-870096 19970605, CIP of US 1998-92317 19980605, US 1999-433621 19991102
FDT AU 2001012944 A Based on WO 200132156; US 6294350 B1 CIP of US 5985592, CIP of US 6025151
PRAI US 1999-433621 19991102; US 1997-870096 19970605; US 1998-92317 19980605
AB WO 200132156 A UPAB: 20010625
NOVELTY - Treating (T) a subject afflicted with a fibroproliferative disease or condition (D/C) characterized by, e.g. increased levels of c-Jun homodimers and increased heterodimerization of c-Jun with another signaling peptide involves administering to the subject, a compound (I), e.g. an antifibrotic and/or antiproliferative agent, effective to ameliorate one or more symptoms of the disease or condition.

DETAILED DESCRIPTION - Treating (T) a subject afflicted with a fibroproliferative disease or condition (D/C) characterized by increased levels of c-Jun homodimers, increased heterodimerization of c-Jun with another signaling peptide, increased levels of phosphorylated c-Jun, and/or increased presence of Jun kinase, involves administering to the subject, a compound (I), e.g. an antifibrotic and/or antiproliferative agent, effective to ameliorate one or more symptoms of the disease or condition.

INDEPENDENT CLAIMS are also included for the following:

(1) an in vitro assay (A1) for identifying whether a test compound is useful for the treatment of a subject afflicted with a fibroproliferative disease, by determining the levels of Jun kinase activity in the presence and absence of the test compound in the test cells maintained in the presence of serum obtained from the subject, where the test cells are fibroblasts, neuroblastomas, glial cells, smooth muscle cells, or cells obtained from the particular organ of interest, and where a reduction of Jun kinase activity in the presence of the test compound, compared to the absence of the test compound, is predictive of the efficacy of the test compound for the treatment of D/C;

(2) an in vitro assay (A2) to determine whether a compound that reduces c-Jun phosphorylation is likely to be effective for treatment of a subject afflicted with a fibroproliferative disease, by determining the uptake by test cells in suitable media, of a labeled building block

indicative of cell proliferation, where the uptake is determined in the presence of serum obtained from the subject, and in the presence and absence of the compound, and where a reduction of uptake by the test cells of the labeled building block in the presence of the test compound, relative to the uptake by the test cells of labeled building block in the absence of the test compound, is predictive of the efficacy of the test compound for the treatment of D/C; and

(3) a kit (K) useful for assays to determine whether a test compound is likely to be effective for treatment of D/C, comprising cultured fibroblasts, glial cells, smooth muscle cells, or cells obtained from the particular organ of interest in a suitable assay medium, a composition containing a predetermined concentration of c-Jun, and one or more labeled building block indicative of cell proliferation.

ACTIVITY - Cytostatic; cerebroprotective; virucide; hepatotropic; protozoacide; nephrotropic; ophthalmological; immunosuppressive; neuroprotective; nootropic; antithyroid; antiinflammatory.

MECHANISM OF ACTION - Blocks c-Jun kinase activity.

Human dermal fibroblasts (F8 cells) were cultured in Dulbecco's modified eagle media supplemented with 5% fetal calf serum. Controls cells were treated with platelet derived growth factor (PDGF) (8 ng/ml) for 2 hours, and test cells were incubated with pentoxifylline (3.5 mM) for 3 hours or 24 hours prior to treatment with the same concentration of PDGF for 2 hours. The cells were then fixed with paraformaldehye, and incubated overnight with a c-Jun specific antibody or a serine 73 phospho specific c-Jun antibody, and then incubated with secondary antibody overnight for detection. The results showed that PDGF effectively increased immunocytochemical staining for c-Jun and serine 73 phosphorylated c-Jun. However, pretreatment with pentoxyfylline reduced the immunoreactivity of the serine 73 phosphorylated c-Jun, indicating that pentoxifylline inhibits the activation of c-Jun to phosphorylated c-Jun.

USE - (I) is useful for treating a subject afflicted with a disease or condition such as breast tumor, fibrosis, squamous cell differentiation, endotoxic shock, multiple sclerosis, squamous cell carcinoma, hepatitis C, cancer, cerebral malaria, renal fibrosis, abdominal adhesions, radiation induced fibrosis, obliterative bronchiolitis, silicosis lesions, Tenon's capsule fibroproliferation, interstitial lung disease, human fibrotic lung disease, human kidney disease, glomerular nephritis, nephritis associated with systemic lupus, peritoneal fibrosis, liver fibrosis, myocardial fibrosis, pulmonary fibrosis, Grave's ophthalmopathy, drug induced ergotism, cardiovascular disease, **Alzheimer**'s disease, scarring, scleroderma, glioblastoma in Li-Fraumeni syndrome, sporadic glioblastoma, myeloid leukemia, acute myelogenous leukemia, myelodysplastic syndrome, myeloproliferative syndrome, gynecological cancer, Kaposi's sarcoma, Hansen's disease, or inflammatory bowel disease not including collagenous colitis, when (I) is pentoxifylline (claimed).

Dwg.0/1

TECH UPTX: 20010625

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: D/C is further characterized by elevation of platelet derived growth factor (PDGF) levels, elevation of c-Jun, activation of NF-kappaB or NF-kappaB p65, neutrophil infiltration, elevated levels of inflammatory cytokine(s), and increased expression of tumor necrosis factor alpha (TNF-alpha).

(T) further involves monitoring the level of phosphorylated c-Jun in serum from the subject, and adjusting the dosage of the compound based on the level detected in the serum of the subject. The labeled building block in A2 is tritiated thymidine.

Preferred Compounds: (I) is any one of the 30 antifibrotic and/or antiproliferative agents given in the specification e.g., hydrocortizone, Losartin, Pirfenidone, nitric oxide, pentifylline and isoniazid,

conjugated-isoniazid, halofuginone, tumor growth factor (TGF)-beta RI/FC, an angiotensi converting enzyme inhibitor, **angiotensin II**, angiotensin 1 receptor **antagonist**, **enalapril**, Octreotide, silyburn marianum, picrohiza kurroa, **captopril**, terbinafine, a combination of pentoxifylline and tocopherol, glycyrrhizin, interferon alpha, phosphatidyl choline, colchicine, tetrandrine, tenidap, decorin, pentifylline, acanthoic acid, polyenylphosphatidylcholine and/or a combination of taurine and niacin.

Preferably (I) is pentoxifylline or a functional derivative or metabolite, e.g. 1-(5-oxohexyl)-3,7-dimethylxanthine (pentoxifylline), 1-(5-hydroxyhexyl)-3,7-dimethylxanthine (metabolite-1) or propentofylline. Preferably, (I) is a c-Jun antisense. (I) is administered in combination with an inhibitor of cytochrome P-450 such as cytochrome P-4501A2, e.g., ciprofloxacin or furafylline, or an inhibitor of kinase. The signaling peptide is CREB, Nrf1 or ATF2.

The disease is further associated with squamous cell carcinoma or fibrosis.

Preferred Cells: The test cells in A2 and (K) are liver myofibroblasts, pulmonary fibroblasts, smooth muscle cells, mesenchymal cells, glial cells, intestinal fibroblasts, intestinal smooth muscle cells, cultured human skin fibroblasts, vascular smooth muscle cells, mesangial cells, hematopoietic cells, Kaposi sarcoma-derived cells or epithelial cells. The test cells comprise a monolayer of cultured human skin fibroblasts or confluent intestinal smooth muscle cells.

Preferred Kit: The labeled building block is tritiated thymidine or bromouridine.

L18 ANSWER 13 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-594404 [56] WPIDS
CR 1999-312396 [26]
DNC C2000-177565
TI Inhibiting first-pass effects of orally administered materials by co-administering with first-pass inhibitors, provides reliable and safe first pass effect inhibition using citrus-based compositions.
DC B02 D13
IN HARRIS, J W
PA (BIOA-N) BIOAVAILABILITY SYSTEMS LLC
CYC 89
PI WO 2000054768 A1 20000921 (200056)* EN 193p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000039977 A 20001004 (200101)
ZA 2001007553 A 20020424 (200237) 192p
ADT WO 2000054768 A1 WO 2000-US2517 20000217; AU 2000039977 A AU 2000-39977 20000217; ZA 2001007553 A ZA 2001-7553 20010913
FDT AU 2000039977 A Based on WO 200054768
PRAI US 1999-251467 19990217
AB WO 200054768 A UPAB: 20020613
NOVELTY - Novel method of inhibiting the first-pass effect of orally administered materials that are subject to a first-pass effect comprises co-administering to the patient the material and a second compound selected from spiro-fused heterocycles (I) or (II).

DETAILED DESCRIPTION - Novel method of inhibiting the first-pass effect of orally administered materials that are subject to a first-pass effect comprises co-administering to the patient the material and a second compound selected from spiro-fused heterocycles of formula (I) or (II).

INDEPENDENT CLAIMS are also included for:

(1) improved methods of designing inhibitors of enzymes or polypeptides, by modification of (I) or (II); and

(2) method for preparing grapefruit juice-derived solids preparations, comprising:

(a) passing grapefruit juice through an initial filter with a filter size at least 200 micro m to produce an initial filtrate; and passing the initial filtrate through a filter with a filter size of 25 - 75 micro m, thereby trapping the grapefruit-derived solids on the filter; or

(b) centrifuging the grapefruit juice at 1000 G for 10 minutes to produce a supernatant and a pellet, optionally resuspending the pellet in water and re-centrifuging to produce a washed pellet of grapefruit-derived solids.

USE - The methods are used to **inhibit** the first-pass effect of orally administered materials that are subject to a first-pass effect (claimed) such as drugs consisting of charged, uncharged, hydrophilic, zwitterionic and/or hydrophobic species including analgesics, antibiotics, antirheumatics, anti-asthmatics, muscle relaxants, narcotic **antagonists**, non-steroidal anti-inflammatory drugs, anesthetics, anti-inflammatories, neuromuscular blockers, sedatives, antimicrobials, anti-arthritics, anticancer agents, aminoglycosides, antifungals, antimalarials, antiparasitics, antituberculars, anti-arrhythmics, antivirals, carbapenems, cephalosporins, fluoroquinolones, macrolides, penicillins, sulfonamides, tetracyclines, cardiovascular agents, cholinergic agonists, **angiotensin II antagonists**, **angiotensin-converting enzyme inhibitors**, protease **inhibitors**, renin **inhibitors**, anti-adrenergic agents, antidysrhythmics, antihyperlipidiemics, antihypotensives, antihypertensives, antiplatelet agents, beta blockers, calcium channel blockers, diuretics, nitrates, pressors, steroids, thrombolytics, contrast media, dermatology agents, antibacterials, endocrine and metabolic agents, androgens/anabolic steroids, bisphosphonates, corticosteroids, chemotherapeutics, anti-diabetics, gout-related agents, minerals, nutritionals, thyroid agents, vitamins, antihistamines, antitussives, decongestants, gastroenterology agents, anti-diarrheals, anti-emetics, anti-ulcer agents, hematology agents, anticoagulants, immunosuppressants, neurological agents, anticonvulsants, antimigraine agents, parkinsonism agents, obstetric and gynecology agents, estrogens, gonadotropin-releasing hormone agonists, appetite suppressants, hormone replacement combinations, labor-induction agents, hormonal agents, progestins, tocolytics, oncology agents, ophthalmology agents, corticosteroids, glaucoma agents, psychiatric agents, **Alzheimer**'s disease agents, antidepressants, tranquilizers, antispasmodics, contraceptives, antimaniacs, antipsychotics, anxiolytics/hypnotics, drug-dependence therapy agents, sympathomimetics, stimulants, anorexiants, receptor agonists, receptor **antagonists**, pulmonary agents, urology agents, bladder spasm agents, erectile dysfunction agents, opioids, nephrolithiasis agents, prostate cancer agents and vasoconstrictors e.g. saquinavir, indinavir, L-deprenyl, tacrolimus, Sandimmune (RTM: cyclosporin A), Neoral, (RTM: cyclosporin A), nelfinavir, VX-478/141 W94, felodipine, nifedipine or sumatriptan as well as ABT-378, acebutolol, acyclovir, aldesleukin, alfentanil, alteplace, amikacin, amphotericin B, amprenavir, anistreplase, atacurium, auranofin, azithromycin, azthreonam, **benazepril**, bisulfan, bleomycin, bretylium, bromocriptine, budesonide, buspirone, capreomycin, carbenicillin, carboplatin, carmustine, carvedilol, cefaclor, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, cephalothin, cephapirin, chlorpromazine, cisplatin, clemastine, cyclosporin, cytarabine, desipramine, didanosine, dobutamine, doxepin, doxorubicin, edrophonium, erythromycin, esmolol,

ethosuximide, felodipine, fentanyl, flumazenil, fluorouracil, foscarnet, **fosinopril**, ganciclovir, gentamicin, heparin, hydralazine, imipramine, indinavir, isradipine, kanamycin, ketamine, labetolol, L-deprenyl, lidocaine, lincomycin, **lisinopril**, lovastatin, nelfinavir, mercaptopurine, methicillin, methohexital, metocurine, metoprolol, mezlocillin, morphine, moxalactam, nabumetone, nadolol, nafcillin, nalbuphine, naloxone, naltrexone, netilmicin, nicardipine, nicotine, nimodipine, nitrendipine, nitroglycerin, norfloxacin, octreotide, oxacillin, paclitaxel, pancuronium, pentamidine, pentoxifylline, pipercuronium, piperacillin, pravastatin, propranolol, pyridostigmine, rifabutin, rimantandine, saquinavir, scopolamine, selegiline, sertraline, simvastatin, spironolactone, streptokinase, streptomycin, sufentanil, sumatriptan, tacrine, tacrolimus, tamoxifen, teniposide, terbutaline, terfenadine, thiopental, ticarcillin, tipranavir, tobramycin, triamcinolone acetonide, tubocurarine, vancomycin, vecuronium, venlafaxine and verapamil.

ADVANTAGE - The methods provide reliable and safe compositions that are citrus-based and contain no, or reduced, amounts of low molecular weight phototoxic furocoumarins. They provide consistent first pass-inhibiting activity. They use first-pass inhibitors (bioenhancers and inhibitors) in non-natural and non-commercially occurring forms.
Dwg.0/2

L18 ANSWER 14 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1997-512420 [47] WPIDS
DNC C1997-163529
TI Composition with **angiotensin II antagonistic** activity - used in combination with agent to increase insulin sensitivity, lower postprandial hyperglycaemia in diabetes mellitus, **inhibit angiotensin converting enzyme**, or **inhibit** HMG-Co A reductase.
DC B02
IN IKEDA, H; SOHDA, T; TAMURA, N; SOHADA, T
PA (TAKE) TAKEDA CHEM IND LTD
CYC 76
PI WO 9737688 A2 19971016 (199747)* DE 62p
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GE GH HU IL IS KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA US UZ VN YU
JP 09323940 A 19971216 (199809) 27p
AU 9721780 A 19971029 (199810)
NO 9804123 A 19980907 (199851)
CZ 9802886 A3 19981216 (199904)
EP 914158 A2 19990512 (199923) EN
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI
SK 9801278 A3 19990507 (199926)
NZ 330774 A 19990629 (199931)
CN 1215338 A 19990428 (199935)
BR 9708517 A 19990803 (199952)
AU 713277 B 19991125 (200006)
HU 9902746 A2 20000528 (200035)
US 6107323 A 20000822 (200042)
MX 9807129 A1 19990301 (200051)
KR 99087076 A 19991215 (200056)
EP 1192951 A2 20020403 (200230) EN
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI

EP 914158 B1 20020710 (200253) EN
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI
US 6432996 B1 20020813 (200255)
DE 69713890 E 20020814 (200261)
RU 2188013 C2 20020827 (200275)
ES 2175385 T3 20021116 (200302)

ADT WO 9737688 A2 WO 1997-JP1149 19970403; JP 09323940 A JP 1997-86484 19970404; AU 9721780 A AU 1997-21780 19970403; NO 9804123 A WO 1997-JP1149 19970403, NO 1998-4123 19980907; CZ 9802886 A3 WO 1997-JP1149 19970403, CZ 1998-2886 19970403; EP 914158 A2 EP 1997-914592 19970403, WO 1997-JP1149 19970403; SK 9801278 A3 WO 1997-JP1149 19970403, SK 1998-1278 19970403; NZ 330774 A NZ 1997-330774 19970403, WO 1997-JP1149 19970403; CN 1215338 A CN 1997-193515 19970403; BR 9708517 A BR 1997-8517 19970403, WO 1997-JP1149 19970403; AU 713277 B AU 1997-21780 19970403; HU 9902746 A2 WO 1997-JP1149 19970403, HU 1999-2746 19970403; US 6107323 A WO 1997-JP1149 19970403, US 1997-836784 19970516; MX 9807129 A1 MX 1998-7129 19980902; KR 99087076 A WO 1997-JP1149 19970403, KR 1998-706462 19980819; EP 1192951 A2 Div ex EP 1997-914592 19970403, EP 2001-124024 19970403; EP 914158 B1 EP 1997-914592 19970403, WO 1997-JP1149 19970403, Related to EP 2001-124024 19970403; US 6432996 B1 Div ex US 1997-836784 19970403, Div ex WO 1997-JP1149 19970403, US 2000-551546 20000418; DE 69713890 E DE 1997-613890 19970403, EP 1997-914592 19970403, WO 1997-JP1149 19970403; RU 2188013 C2 WO 1997-JP1149 19970403, RU 1998-119885 19970403; ES 2175385 T3 EP 1997-914592 19970403

FDT AU 9721780 A Based on WO 9737688; CZ 9802886 A3 Based on WO 9737688; EP 914158 A2 Based on WO 9737688; NZ 330774 A Based on WO 9737688; BR 9708517 A Based on WO 9737688; AU 713277 B Previous Publ. AU 9721780, Based on WO 9737688; HU 9902746 A2 Based on WO 9737688; US 6107323 A Based on WO 9737688; KR 99087076 A Based on WO 9737688; EP 1192951 A2 Div ex EP 914158; EP 914158 B1 Related to EP 1192951, Based on WO 9737688; US 6432996 B1 Div ex US 6107323; DE 69713890 E Based on EP 914158, Based on WO 9737688; RU 2188013 C2 Based on WO 9737688; ES 2175385 T3 Based on EP 914158

PRAI JP 1996-83917 19960405

AB WO 9737688 A UPAB: 19971217

Composition comprises a compound having **angiotensin II antagonistic** activity (I) in combination with at least one compound with the activity of: (i) increasing insulin sensitivity (Ia); (ii) lowering postprandial hyperglycaemia in diabetes mellitus (Ib); (iii) **inhibiting angiotensin converting enzyme** (by means of an indane derivative) (Ic); or (iv) **inhibit** HMG-Co A reductase (by means of a pyridine derivative) (Id).

USE - The compositions are used to treat angiotensin II mediated disease, especially those of the circulatory system, and in particular hypertension, cardiac insufficiency, cerebral apoplexy, ischemic peripheral circulation disturbances, myocardial ischaemia, venous insufficiency, progressive cardiac insufficiency after myocardial infarction, diabetic nephropathy, nephritis, glomerulonephritis, arteriosclerosis, angiohypertrophy, vascular hypertrophy or obstruction after percutaneous transluminal coronary angioplasty, vascular re-obstruction after bypass surgery, hyperaldosteronism, glomerulosclerosis, renal insufficiency, glaucoma, occular hypertension, hyperlipaemia, myocardial infarction, angina pectoris, aneurysm, coronary arteriosclerosis, cerebral arteriosclerosis, peripheral arteriosclerosis, thrombosis, diseases of central nervous system, **Alzheimer**'s disease, deficiency of memory, depression, amnesia, **senile dementia**, sensory disturbances, multiple system organ failure or scleroderma, or to prevent or ameliorate anxiety neurosis, catatonia,

and indisposition or dyspeptic symptoms (all claimed).
Dwg.0/0

L18 ANSWER 15 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1993-405707 [50] WPIDS
DNC C1993-180286
TI New phosphorus contg. heterocyclic cpds. as angiotensin antagonists - useful for treating e.g. hypertension, congestive heart failure and hyperaldosteronism.
DC B02 B03
IN GIBSON, K H
PA (ZENE) ZENECA LTD
CYC 41
PI WO 9324501 A1 19931209 (199350)* 50p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AT AU BB BG BR CA CH CZ DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO NZ PL PT RO RU SD SE SK UA US
AU 9340840 A 19931230 (199415)
ADT WO 9324501 A1 WO 1993-GB1068 19930524; AU 9340840 A AU 1993-40840 19930524
FDT AU 9340840 A Based on WO 9324501
PRAI GB 1992-11292 19920528
AB WO 9324501 A UPAB: 19940203
P-contg. heterocyclic derivs. of formula (I) and their non-toxic salts and metabolically labile esters are new. Where Q = a gp. of formula (i)-(v); ring B completes a benzene or pyridine ring; R1,T1,F1 = 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-4C alkyl), Ph, Ph(1-4C alkyl) or 1-4C alkyl substd. with 1 or more F or 1-4C alkoxy; R2,T2,F2 = H, 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-4C alkyl), carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, CN, NO2, Ph or Ph(1-4C alkyl); R3,R4 opt. = 1-4C alkyl, 1-4C alkoxy, halogen, CF3, CN, NO2, fluoro(1-4C alkoxy), OH or hydroxy(1-4C alkyl); T3 = halogen, 1-4C alkoxy, NH2, 1-6C alkylamino or di(1-6C alkyl)amino, or as defined for T1; T4,F3 = H, 1-4C alkyl, 1-4C alkoxy, 1-4C alkyl substd. with 1 or more F, carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, halogen, CN, NO2, carbamoyl, 1-4C alkanoyl, N-(1-7C alkyl)carbamoyl, di(N-1-7C alkyl)carbamoyl, NH2, 1-6C alkylamino or di(1-6C alkyl)amino or -A1.B1; or T3 and T4 together form 3-6C alkenylene, 3-6C alkylene opt. with a methylene replaced by carbonyl, provided that when T3 and T4 form one of these, then T2 is additionally selected from a value defined for T4; B1 = a) Ph opt. substd. with one or two 1-4C alkyl, 1-4C alkoxy, halogen, CN, CF3, NO2, OH, carboxy, 1-4C alkanoylamino, 1-4C alkanoyl, fluoro(1-4C alkoxy), hydroxy(1-4C alkyl), etc.; Y = O or -NRb-; Rb = H, 1-4C alkyl, 1-4C alkanoyl or benzoyl; A = -CH=CH-, -CH=CH-CO-, -CO-CH=CH-, -CO-CH2-CH2-, -CH2-CH2-CO, -CH2-CO- or -CO-CH2-; E1 = H, 1-8C alkyl or CF3; E2 = H, 1-8C alkyl, halogen, 1-4C alkoxy, CF3, carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, CN, NO2, 1-4C alkanoyl, 1-4C alkyl.S(O)m- or phenylsulphonyl; m = 0-2; E3 = H, 1-8C alkyl, 1-4C alkoxy, halogen or CF3; E4,E5 opt. = 1-4C alkyl opt. substd. with one or more F, Ph, pyridyl, alkoxy, halogen, CN, NO2, carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, carbamoyl, N-(1-7C alkyl)carbamoyl, di-(N-1-7C alkyl)carbamoyl, 1-4C alkylthio, 1-4C alkylsulphinyl, 1-4C alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl or 1-4C alkanoyl; L1 = 1-8C alkyl; L2,L3 = H or 1-4C alkyl; F4 = H or 1-4C alkyl; or F2 and F3 together form a benzene ring opt. substd. with 1 or 2 substits. selected from values defined for F3; or 3-6C alkyenylene; or 3-6C alkylene opt. with a methylene replaced by carbonyl; or F3 and F4 together form A2; A2 = -CH2-CH2-, -CH2-CH2-CH2-, -CO-CH2-, -CH2-CO-, -CO-CH2-CH2-, -CH2-CH2-CO-, -CO-CH=CH- or -CH=CH-CO-, each being opt. substd. by 1 or 2 substits. selected from values defined for E4 or E5; X = methylene or a direct bond; Rm,Rn = H, 1-4C alkyl, 1-4C alkoxy, halogen, CF3, CN or NO2; any Ph moieties of

R1,R2,T1,T2,T3,E2,E4,E5,F1 or F2 may be opt. substd. with 1 or 2 substits. selected from 1-4C alkyl, 1-4C alkoxy, halogen, CN and CF3.

Also new are intermediates of formula (V): G1 = 1-6C alkyl, Ph or benzyl; Hal = a leaving gp.

USE - (I) are **angiotensin II antagonists**, useful for treating hypertension, congestive heart failure and/or hyperaldosteronism, also ocular hypertension, glaucoma, cognitive disorders (e.g. **Alzheimer**'s disease, amnesia, **senile dementia** and learning disorders), renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and mental illnesses (e.g. schizophrenia). (I) may be administered together with another pharmacological agent, e.g. beta-adrenergic blocker, Ca channel blocker, **ACE inhibitor** or diuretic. Daily oral dosage of (I) is up to 50 mg/kg, pref. up to 10 mg/kg, and parenteral dosage up to 5mg/kg, pref. up to 1 mg/kg.

Dwg.0/0

L18 ANSWER 16 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1993-405695 [50] WPIDS
DNC C1993-180274
TI New nitrogen contg. heterocyclic cpds. as **angiotensin II antagonists** - useful for treating e.g. hypertension, congestive heart failure and hyperaldosteronism.
DC B02 B03
IN GIBSON, K H
PA (ZENE) ZENECA LTD
CYC 41
PI WO 9324487 A1 19931209 (199350)* EN 48p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AT AU BB BG BR CA CH CZ DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO NZ PL PT RO RU SD SE SK UA US
AU 9340834 A 19931230 (199415)
ADT WO 9324487 A1 WO 1993-GB1057 19930521; AU 9340834 A AU 1993-40834 19930521
FDT AU 9340834 A Based on WO 9324487
PRAI GB 1992-11270 19920528
AB WO 9324487 A UPAB: 19940203

N-contg. heterocyclic derivs. of formula (I) and their non-toxic salts and metabolically labile esters are new. Where, Q = a gp. of formula (i)-(V): ring B completes a benzene or pyridine ring; R1, T1, F1 = 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-4C alkyl), Ph, Ph(1-4C alkyl) or 1-4C alkyl substd. with 1 or more F or 1-4C alkoxy; R2, T2, F2 = 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-4C alkyl), carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, CN, NO2, Ph or Ph(1-4C alkyl); R3, R4 opt. = 1-4C alkyl, 1-4C alkoxy, halogen, CF3, CN, NO2, fluoro(1-4C alkoxy), OH or hydroxy(1-4C alkyl); T3 = halogen, 1-4C alkoxy, NH2, 1-6C alkylamino or di(1-6C alkyl)amino, or as defined for T1; T4, F3 = H, 1-4C alkyl, 1-4C alkoxy, 1-4C alkyl substd. with 1 or more F, carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, halogen, CN, NO2, carbamoyl, 1-4C alkanoyl, N-(1-7C alkyl)carbamoyl, di(N-1-7C alkyl)carbamoyl, NH2, 1-6C alkylamino off di(1-6C alkyl)amino or -A1.B1; or T3 and T4 together form 3-6C alkenylene, 3-6C alkylene opt. with a methylene replaced by carbonyl, provided that when T3 and T4 form one of these, then T2 is additionally selected from a value defined for T4; B1 = Ph opt. substd. with one or two 1-4C alkyl, 1-4C alkoxy, halogen, CN, CF3, NO2, OH, carboxy, 1-4C alkanoylamino, 1-4C alkanoyl, fluoro(1-4C alkoxy), hydroxy(1-4C alkyl), etc., n = 0-2; Y = O or -NRb-; Rb = H, 1-4C alkyl, 1-4C alkanoyl or benzoyl; A = -CH=CH-, -CH=CH-CO-, -CO-CH=CH-, -CO-CH2-CH2-, -CH2-CH2-CO, -CH2-CO- or -CO-CH2-; E1 = H, 1-8C alkyl or CF3; E2 = H, 1-8C alkyl, halogen, 1-4C alkoxy, CF3, carboxy, 1-4C alkoxycarbonyl, 3-6C

alkenyloxycarbonyl, CN, NO2, 1-4C alkanoyl, 1-4C alkyl.S(O)m- or phenylsulphonyl; m = 0-2; E3 = H, 1-8C alkyl, 1-4C alkoxy, halogen or CF3; E4, E5 opt. = 1-4C alkyl opt. substd. with one or more F, Ph, pyridyl, alkoxy, halogen, CN, NO2, carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, carbamoyl, N-(1-7C alkyl)carbamoyl, di-(N-1-7C alkykl)carbamoyl, 1-4C alkylthio, 1-4C alkylsulphinyl, 1-4C alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl or 1-4C alkanoyl; L1 = 1-8C alkyl; L2, L3 = H or 1-4C alkyl; F4 = H or 1-4C alkyl; or F2 and F3 together form a benzene ring opt. substd. with 1 or 2 substits. selected from values defined for F3; or 3-6C alkyenylene; or 3-6C alkylene opt. with a methylene replaced by carbonyl; or F3 and F4 together form A2; A2 = -CH2-CH2-, -CH2-CH2-CH2-, -CO-CH2-, -CH2-CO-, -CO-CH2-CH2-, CH2-CH2-CO-, -CO-CH=CH- or -CH=CH-CO, each being opt. substd. by 1 or 2 substits. selected from values defined for E4 or E5; Rm, Rn = H, 1-4C alkyl, 1-4C alkyl, 1-4C alkoxy, halogen, CF3, CN or NO2; any Ph moieties of R1,R2,T1,T2,E2,E4,E5,F1 or F2 may be opt. substd. with 1 or 2 substits. selected from 1-4C alkyl, 1-4C alkoxy, halogen, CN and CF3.

3-(4-(5,7-diethyl-2-oxo- 1,2-dihydro-1,6-naphthyridin -1-ylmethyl)phenylcarbamoyl -3-phenylpropenoic acid (1a).

USE - (I) are **angiotensin II antagonists**, useful for treating hypertension, congestive heart failure and/or hyperaldosteronism, also ocular hypertension, glaucoma, congnitive disorders (e.g. **Alzheimer**'s disease, amnesia, **senile dementia** and learning disorders), renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and mental illnesses (e.g. schizophrenia). (I) may be administered together with another pharmacological agent, e.g. beta-adrenergic blocker, Ca channel blocker, **ACE inhibitor** or diuretic. The daily oral dosage of (I) is up to 50 mg/kg, pref. up to 10 mg/kg, and parenteral dosage up to 5 mg/kg, pref. up to 1 mg/kg.

Dwg.0/0

L18 ANSWER 17 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1993-385686 [48] WPIDS
CR 1991-266884 [36]; 1991-266886 [36]; 1993-287706 [36]; 1995-335853 [42]
DNC C1993-171480
TI New N-benzyl-quinazolinone derivs. - used e.g. as **angiotensin II antagonists**, antihypertensives, CNC drugs and anti-dopaminergic agents.
DC B02
IN DHANOA, D S; FITCH, K J; GREENLEE, W J; HANGAUER, D; PATCHETT, A A; RIVERO, R A; WALSH, T F
PA (MERI) MERCK & CO INC
CYC 1
PI US 5264439 A 19931123 (199348)* 65p
ADT US 5264439 A Cont of US 1990-479786 19900213, CIP of US 1991-671552 19910319, US 1991-744138 19910813
PRAI US 1991-744138 19910813; US 1990-479786 19900213; US 1991-671552 19910319
AB US 5264439 A UPAB: 19951109
3-(4-susbtd. benzyl)- quinazolin-4(3H)-ones or 1-(4-substd. benzyl)-quinazolin-4(1H)-ones of formula (I) and their salts are new. Het = quinazolinone gp. of formula (A1) or (A2). R'' = 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl (all opt. substd. by Ar, 3-7C cycloalkyl, Cl, Br, I, F, OH, NH2, NHQ, NQ2, NHSO2R2, CF3, COOR2 or SO2NHR2a); or Ar; Ar = phenyl or naphthyl, both opt. substd. Q = 1-4C alkyl; E = direct bond; R2 = H or 1-6C alkyl; R2a = R2, benzyl or phenyl; R7a, R7b = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, Cl, Br, I, F or CF3; R8a, R8b = H, Ar-substd. Q, opt. substd. 1-6C alkyl, -COAr, 3-7C cycloalkyl, Cl, Br, I, F etc. n =

0-2; R9,R10 = H, 1-6C alkyl (opt. substd. by 3-7C cycloalkyl), 2-6C alkenyl, 2-6C alkynyl, Cl, Br, F, I, 1-6C alkoxy, 1-6C perfluoroalkyl, etc. or R9 + R10 on adjacent C = fused phenyl ring; X = O; S(O)n, NR13, CH2O, CH2S(O)n, CH2NR13, OCH2, NR13CH2, S(O)nCH2, CH2, CH2CH2 or direct bond; or -X-CR12Z-YR12 = -CH=CR12Z; Y = direct bond, O, S(O)n, NR13 or CH2; provided that X and Y are defined such that the C atom to which Z is bonded is not simultaneously bonded to two heteroatoms (O,N,S,SO,SO2); R11, R12 = H; 1-6C alkyl (opt. substd.); or aryl or aryl-(1-2C) alkyl (both opt. substd.). Z = COOH or COOR24; R13 = H, 1-6C alkyl, aryl, aryl (1-6C alkyl) (C=O) etc. R24 = Q, -CHR25-O-COR26, -CH2CH2-N(1-2C alkyl), or -(CH2CH2O)y-O-Q (sic); Ar or CH2Ar (in both of which Ar is opt. substd. by COOQ); or 2-oxo-5-methyl-1,3-dioxolen-4-ylmethyl, phthalidyl, indan-5-yl or 2,2-dimethyl-1,3-dioxolan-4-ylmethyl; y = 1 or 2; R25, R26 = 1-6 alkyl or pH.

USE - (I) are **angiotensin (II) antagonists** and are useful for treatment of hypertension (claimed), congestive heart failure, ocular hypertension (claimed), sec. hyperaldosteronism, pulmonary hypertension or hyperaldosteronism, renal failure, etc. (I) also have CNS activity and are useful for treatment of cognitive dysfunctions (e.g. **Alzheimer**'s disease, amnesia or **senile dementia**), anxiety, tension, depression or dysphoric mental states. (I) have anti-dopaminergic properties, and are useful for treating dopamine dysfunction disorders such as schizophrenia. (I) are esp. used as antihypertensives at daily doses of 1-1000 (pref. 2.5-75) mg, orally or parenterally, opt. in combination with other antihypertensives, diuretics, **ACE inhibitors** and/or calcium channel blockers.

Dwg.0/0

Dwg.0/0

L18 ANSWER 18 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1993-054274 [07] WPIDS
DNC C1993-024287
TI New quinoline and naphthyridine derivs. as **angiotensin II antagonist** - for treating hypertension, heart failure, hyperaldosteronism, renal failure, diabetic retinopathy, migraine, atherosclerosis, cognitive disorders etc..
DC B02
IN CHAKRAVARTY, P K; GREENLEE, W J
PA (MERI) MERCK & CO INC
CYC 10
PI EP 527534 A1 19930217 (199307)* EN 45p
R: CH DE FR GB IT LI NL
CA 2075652 A 19930214 (199318)
US 5246944 A 19930921 (199339) 24p
JP 06056789 A 19940301 (199413) 30p
ADT EP 527534 A1 EP 1992-202422 19920805; CA 2075652 A CA 1992-2075652 19920810; US 5246944 A US 1991-744140 19910813; JP 06056789 A JP 1992-215991 19920813
PRAI US 1991-744140 19910813
AB EP 527534 A UPAB: 19940126
Substd. benzyloxy- quinoline and 1,5-naphthyridine derivs. of formula (I) and their salts are new.

In (I) R1 = H, 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl (1-4C alkyl), 1-8C perfluoroalkyl, Ph or Ph (1-4C alkyl); R2 = H, 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl (1-4C alkyl), CO2R5a, 1-4C alkoxycarbonyl, CN, NO2, Ph or Ph (1-4C alkyl); R3, R4 = H, 1-6C alkyl opt.substd. by 1 of Ph, naphthyl, 3-7C cycloalkyl, NR5R21, morpholin-4-yl, OH, CO2R5a or CON(R5)2), 1-6C alkoxy, 1-4C perfluoroalkoxy, halo, CF3, CN, NO2, OH, NH2, NH (1-6C alkyl), N(1-6C alkyl)2, N(CH2CH2)2O,

N(CH2CH2)2NCOR5a, N(CH2CH2)2NR5a, CO2R5a, CONH2, 1-4C alkoxycarbonyl, CONH(1-7C alkyl) or CON(1-7C alkyl)2; or R3 + R4 = 1-4C alkylenedioxy; x = 0-2; m = 1-5; n = 1-10; E = CH or N; R5 = H or 1-6C alkyl; R5a = R5, CH2Ph, CH2-naphthyl, Ph or naphthyl; R9, R10 = H, 1-6C alkyl (opt. substd. by 3-7C cycloalkyl), 2-6C alkenyl, 2-6C alkynyl, halo, 1-6C alkoxy, 1-6C perfluoroalkyl, 3-7C cycloalkyl, Ph, naphthyl, 1-6C alkyl-S(O)x-(Ch2)n, HO(1-6C alkyl) CF3, CO2R5a, Oh, NR5R21, 1-6C alkyl-NR5R21, NO2, (CH2)n-SO2-N(R5)2, NR5CO(1-4C alkyl) or CON(R5)2; or R9 + R10, when on adjacent C atoms, = Ph; X = O, S(O)x, NR13, CH2O, CH2S(O)x, CH2NR13, OCH2, NR13CH2, S(O)xCH2, CH2, (CH2)2 or a bond; or X = -CH=, in which case Y and R12 are absent; Y = a bond, O, S(O)x, NR13 or CH2; provided that the C to which Z is attached is not bonded to 2 heteroatoms; R11, R12 = H, 1-6C alkyl (opt. substd. by 1 of Ph, naphthyl, NR5R21, 3-7C cycloalkyl, morpholin-4-yl, OH, CO2R5a or CON(R5)2), Ph, naphthyl, Ph (1-2C alkyl) or naphthyl (1-2C alkyl) (all opt. substd. by 1-3 from halo, 1-6C alkyl, 1-5C alkenyl-CH2, 1-5C alkynyl-CH2, 1-6C alkyl-S(O)n(CH2)n, CF3, CO2R5a, OH, NR5R21, NO2, NR5COR5, CON(R5)2, G(1-6C alkyl)R23, N(CH2CH2)2Q3 and P(O)(O(1-4C alkyl))2, and additionally opt. substd. by 1-2 from Br, Cl and F) or 3-7C cycloalkyl. New compsn. comprises (I), a carrier and opt. another anti-hypertensive agent (diuretic, **ACE inhibitor**, Ca channel blocker or beta-blocker) (amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and tannates, deserpidine, diazoxide, guanethidene sulphate, hydralazine HCl, hydrochlorothiazide, metolazone, metoprolol tartrate, methyclothiazide, methyldopa, methyldopate.HCl, minoxidil, pargyline HCl, polythiazide, prazosin, propranolol, rauwolfia serpentina, rescinnamine, reserpine, sodium nitroprusside, spironolactone, timolol maleate, trichlormethiazide, trimethophan camsylate, benzthiazide, quinethazone, ticrynafen, triamterine, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynate, **captopril**, delapril.HCl, **enalapril**, enalaprilat, **fosinopril** Na, **lisinopril**, pentopril, **quinapril** HCl, **ramipril**, teprotide zofenopril Ca, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, etc, and admixtures and combinations of these.

USE - (I) are **angiotensin II antagonists** and are useful for treating hypertension, acute and chromic congestive heart failure, secondary hyper aldosteronism, prim. and sec. pulmonary hyperaldosteronism, prim. and sec. pulmonary hypertension, renal failure e.g. diabetic nephropathy, glomerulonephritis, sclerodema, glomerular sclerosis, proteinuria of prim. renal disease, end stage renal disease renal transplant therapy etc, renal vascular hypertension, left ventricular dysfunction, diabetic retinopathy and vascular disorders e.g. migraine, Raynaud's disease, luminal hyperplasia, and to minimise atherosclerosis. (I) are also useful for treating ocular hypertension. In addition, (I) have CNS activity and are useful in the treatment of cognitive dysfunction (e.g. **Alzheimer**'s disease, amnesia and **senile dementia**) and to relieve anxiety and tension in patients with depressed or dysphoric mental states. (I) also have antidopaminergic activity and are useful to treat disorders involving dopamine dysfunction (e.g. schizophrenia). Admin. is oral, rectal, parenteral or (for ocular treatment), topical, at a daily dose of 1-1000 mg, pref. 2.5-250 mg, esp. 2.5-75 mg (cardiovascular and ocular disorders) or 5-6000 mg, pref. 10-4000 mg, esp. 20-2000 mg (CNS disorders), opt. in divided doses.

Dwg.0/0

Dwg.0/0

L18 ANSWER 19 OF 23 WPIDS (C) 2003 THOMSON DERWENT

AN 1993-001518 [01] WPIDS
DNC C1993-000618
TI New heterocyclic derivs. are **angiotensin II antagonists** - for treating hypertension, congestive heart failure, cognitive disorders, post-myocardial infarction, anxiety, schizophrenia, etc..
DC B02
IN BRADBURY, R H; THOMAS, A P
PA (ICIL) IMPERIAL CHEM IND PLC
CYC 19
PI EP 520723 A1 19921230 (199301)* EN 34p
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE
CA 2071021 A 19921226 (199316)
EP 520723 B1 19940601 (199421) EN 40p
R: AT BE CH DE DK FR GB IT LI LU MC NL PT SE
JP 06145170 A 19940524 (199425) 30p
DE 69200160 E 19940707 (199427)
US 5387592 A 19950207 (199512) 20p
ADT EP 520723 A1 EP 1992-305704 19920622; CA 2071021 A CA 1992-2071021 19920611; EP 520723 B1 EP 1992-305704 19920622; JP 06145170 A JP 1992-165963 19920624; DE 69200160 E DE 1992-600160 19920622, EP 1992-305704 19920622; US 5387592 A US 1992-904227 19920625
FDT DE 69200160 E Based on EP 520723
PRAI GB 1991-13628 19910625
AB EP 520723 A UPAB: 19931118
Heterocyclic derivs. of formula (I) and their salts are new. B = benzene or pyridine; R1, T1 = 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-4C alkyl), Ph, phenyl-(1-4C alkyl) or 1-4C alkyl substd. by 1-4C alkoxy or 1 or more F; R2, T2 = H, 1-8C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-4C alkyl), CO2H, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, CN, NO2, Ph or phenyl-(1-4C alkyl); R3, R4 opt. = 1-4C alkyl, 1-4C alkoxy, halo, CF3, CN, NO2, F-(1-4C alkoxy), OH or HO-(1-4C alkyl); T3 = T1, halo, 1-4C alkoxy, NH2, NH(1-6C alkyl) or N(1-6C alkyl)2; T4 = H, 1-4C alkyl (opt. substd. 1-4C alkoxy, CO2H, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, halo, CN, NO2; A1 = 1-6C alkylene, C=O or a bond; B1 = Ph (opt. substd. by 1-2 from 1-4C alkyl, 1-4C alkoxy, halo, CN, CF3, NO2, OH, CO2H, 1-4C alkanoylamino, 1-4C alkanoyl; n = 0-2; or T3 + T4 = 3-6C alkenylene or 3-6C alkylene (opt. with CH2 replaced by CO), in which case T2 may also be any T4; Y = O or NRb; Rb = H, 1-4C alkyl, 1-4C alkanoyl or benzoyl; A = CH=CH, CH=CH-CO, CO-CH=CH, CO-(CH2), (CH2)2CO, CH2CO or COCH2; E1 = H, 1-8C alkyl or CF3; E2 = H, 1-8C alkyl, halo, 1-4C alkoxy, CF3, CO2H, 1-4C alkoxycarbonyl; E3 = H, 1-8C alkyl, 1-4C alkoxy, halo or CF3; E4, R5 opt. = 1-4C alkyl (opt. substd.) Ph, pyridyl, alkoxy, halo, CN, NO2, CO2H, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl; L1 = 1-8C alkyl; L2, L3 = H or 1-4C alkyl; X = O, S or NRc; Rc = H or 1-4C alkyl; Ra = H, 1-4C alkyl, 1-4C alkoxy, halo, CF3, CN or NO2; Z = 1H-tetrazol-5-yl, CO2H or CF3SO2NH; Ph gps. of R1, R2, T1-T3 and E2 are opt. substd. by 1-2 from 1-4C alkyl, 1-4C alkoxy, halo, CN and CF3.

USE - (I) are **angiotensin II** (AII) **antagonists** useful in the treatment of hypertension, congestive heart failure, hyperaldosteroism and other disease states involving the renin-angiotensin-aldosterone system. (I) may also be useful for the treatment of ocular hypertension, glaucoma, cognitive disorders (e.g. **Alzheimer**'s disease, amnesia, **senile dementia** and learning disorders) and other diseases (e.g. renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and certain mental illnesses (e.g. schizophrenia)). Admin. is oral (at a daily dose of upto 50 mg/kg, pref. up to 10 mg/kg) or parenteral (at a daily dose of up to 5 mg/kg, pref. up to 1 mg/kg). (I) may be administered with another agent e.g. a beta-blocker,

Ca-channel-blocker, **ACE inhibitor** or diuretic.
0/0
li
Dwg.0/0

L18 ANSWER 20 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1992-375128 [46] WPIDS
CR 1995-301570 [39]
DNC C1992-166428
TI New substituted quinazolinone(s) are **angiotensin II antagonists** - for treating hypertension, **Alzheimer**'s disease, depression, etc..
DC B03
IN CHAKRAVARTY, P K; DE, LASZLO S E; GLINKA, T W; GREENLEE, W J; KIM, D; MANTLO, N B; PATCHETT, A A; DOOSEOP, K
PA (MERI) MERCK & CO INC
CYC 10
PI EP 512870 A1 19921111 (199246)* EN 119p
R: CH DE FR GB IT LI NL
CA 2068229 A 19921111 (199305)
JP 05155867 A 19930622 (199329) 80p
US 5238942 A 19930824 (199335) 58p
ADT EP 512870 A1 EP 1992-304215 19920511; CA 2068229 A CA 1992-2068229 19920508; JP 05155867 A JP 1992-117670 19920511; US 5238942 A CIP of US 1991-698506 19910510, US 1992-867794 19920416
PRAI US 1992-867794 19920416; US 1991-698506 19910510
AB EP 512870 A UPAB: 19951011
Quinazolones of formula (I) and their salts are new, where L is connected to J or K to form an aromatic ring. J = C=M, or JL together form a 6C ring (substd. by R7a, R7b, R8a and R8b); K = C=M, or KL together form a 6C ring (substd. as JL); M = O or NR22; R1 = e.g. SO2NR25OR25, SO2NHSO2R23, SO2NHCOOR23, etc.; R2a, R2b = e.g. H, halo, NO2, NH2, mono- or di- (1-4C alkyl)amino, CF3, 1-6C alkyl, 2-7C alkyl(thio)methyl, 2-6C alkynyl, Ar, Ar1-4C alkyl, etc.; Ar = phenyl or naphthyl (opt. substd. by 1 or 2 of e.g. halo, 1-4C alkyl, 1-4C alkoxy,NO2,CF3, 1-4C alkylS(O)x, etc.); R3a = H, halo, 1-6C alkyl, 1-6C alkoxy, or 1-6C alkoxyalkyl; R3b = e.g. H, halo, NO2, 1-6C alkyl, 1-6Cacyloxy, 3-7C cycloalkyl, 1-4C hydroxyalkyl, Ar1-4C alkyl, mono- or di- (1-4Calkyl)amino, 1-4C fuloroalkyl, etc.; E = a bond, NR13(CH2)s, S(O)x(CH2)s, CHOH, O or CO; x = 0-2; s = 0-5; R7a, R7b = H, 1-6C alkyl, 2-6C alkenyl, or 2-6C alkynyl, halo, or CF3; or R5aCCR7b together = phenyl; R8a, R8b = H, 1-6C alkyl (opt. substd. by e.g. OH, guanidino, 1-4C alkoxy, tetrazol-5-yl, CONHSO2R23, (1-6C alkyl)piperazino, COAr, 3-7C cycloalkyl, halo, OH, OR23, etc.); R13 = H, 2-5C acyl, 1-6C alkyl, allyl, 3-6C cycloalkyl, Ar, or ArCH2; R22 = e.g. Ar, or 1-4C alkyl (opt. substd. by e.g. Ar, OH, NH2, mono- or di- (1-4Calkyl)amino, COOR4, halo or CF3); R23 = e.g. Ar, 3-7C cycloalkyl, 1-6C alkyl (opt. substd. by e.g. Ar, 1-4C alkoxy, CF3, halo, NO2, COOH, 2-5C alkoxycarbonyl, NH2, PO3H2, etc.); R25 = H, Ar, or 1-6C alkyl (opt. substd. by Ar, F, Cl, Br, OH, NH2, mono- or di- (1-4C alkyl)amino, or CF3); X = e.g. a bond, CO, O,S, NR13, OCH2, CH2O, SCH2, CH2S, CF=CF, CHG=CH, 1,2-cyclopropylene, etc.). and r = 1 or 2.

USE - (I) are **angiotensin II antagonists** useful in the treatment of hypertension, intraocular pressure, and congestive heart failure. Compsns. opt. include a second antihypertensive agent selected from a diuretic, **angiotensin converting enzyme inhibitor**, Ca channel blocker, or beta-blocker. Dosage alone is 1-1000, pref. 2.5-250, more pref. 5-150 mg/day. (I) also have CNS activity, and are useful in the treatment of cognitive dysfunctions including **Alzheimer**'s disease, amnesia, or **senile dementia**. They also have anxiolytic and

antidepressant properties and are useful in the relief of anxiety and tension symptoms, or the treatment of patients with depressed or dysphoric mental states. (I) show antidopaminergic properties, useful to treat disorders of dopamine dysfunction including schizophrenia.
Dwg. 0/0
Dwg. 0/0

L18 ANSWER 21 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1992-367611 [45] WPIDS
DNC C1992-163246
TI New pyrrolo pyridine derivs. - used as **angiotensin II antagonists** for treatment of hypertension and congestive heart failure.
DC B02
IN EDWARDS, M P; MASEK, B B; PEARCE, R J
PA (ICIL) IMPERIAL CHEM IND PLC; (ZENE) ZENECA LTD
CYC 20
PI EP 511791 A2 19921104 (199245)* EN 34p
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE
AU 9214072 A 19921105 (199252)
CA 2066005 A 19921031 (199303)
ZA 9202557 A 19930127 (199310) 55p
JP 05140161 A 19930608 (199327) 31p
EP 511791 A3 19930127 (199347)
ADT EP 511791 A2 EP 1992-303712 19920424; AU 9214072 A AU 1992-14072 19920407; CA 2066005 A CA 1992-2066005 19920414; ZA 9202557 A ZA 1992-2557 19920408; JP 05140161 A JP 1992-111744 19920430; EP 511791 A3 EP 1992-303712 19920424
PRAI GB 1991-9246 19910430
AB EP 511791 A UPAB: 19950619
Pyrrolopyridine derivs. of formula (I) and their N-oxides are new. In (I), R1 is H, 1-8C alkyl; 3-8C cycloalkyl; Ph; substd. 1-4C alkyl contg. 1 or more F substits. or 3-8C cycloalkyl, 1-4C alkoxy or Ph; R2 is H, 1-4C alkyl, 1-4C alkoxy, halogen, CF3, carboxy, 1-4C alkoxycarbonyl, 3-6C alkenyloxycarbonyl, CN, NO2, carbamoyl, 1-4C alkanoyl, N-alkylcarbamoyl or di(N-alkyl) carbamoyl of up to 7C, NH2, alkylamino or dialkylamino of up to 6C, 3-(1-4C)alkylureido or 1-4C alkanoylamino; R3 is halogen, 1-4C alkoxy, OH, NH2, alkylamino or dialkylamino of up to 6C, or as defined for R1; R4 is H, 1-4C alkyl opt. contg. 1 or more F, 1-4C alkoxy, halogen, carboxy, 1-4C alkoxy-carbonyl, 3-6C alkenyloxycarbonyl, CN, NO2, 1-4C alkanoyl, 1-4C alkylthio, 1-4C alkylsulphinyl, 1-4C alkylsulphonyl or phenylsulphonyl; R5 is H, 1-8C alkyl, 1-4C alkyl contg. 1 or more F, OH(1-4C)alkyl, carboxy, 1-4C alkoxy-carbonyl, 3-6C alkenyloxycarbonyl, CN, 1-4C alkanoyl, 1-4C alkylthio, 1-4C alkylsulphinyl, 1-4C alkylsulphonyl, phenylsulphonyl, 3-8C cycloalkyl, 3-8C cycloalkyl(1-4C)alkyl, Ph or Ph(1-4C)alkyl; R6 is H, 1-4C alkyl, 1-4C alkoxy, halogen, CF3, CN or NO2; X is phenylene opt. substd. with 1-4C alkyl, 1-4C alkoxy, halogen, 1-4C alkanoyl, CF3, CN or NO2, or X is a direct bond between adjacent Ph and methylene gps. Z is 1H-tetrazol-5-yl, -CO.NH.(1H-tetrazol-5-yl), -CO.OR7 or -CO.NH.SO2R8; R7 is a non-toxic biodegradable residue of a physiologically acceptable alcohol or phenol; R8 is 1-6C alkyl, 3-8C cycloalkyl or Ph; Ph moieties being opt. substd. with 1 or 2 substituents selected from 1-4C alkyl, 1-4C alkoxy, halogen, CN or CF3.
USE - (I) are **angiotensin II antagonists**, useful in the treatment of e.g. hypertension, congestive heart failure and/or hyperaldosteronism, and also ocular hypertension, glaucoma, cognitive disorders (e.g. **Alzheimer**'s disease amnesia, **senile dementia** and learning disorders), renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and schizophrenia. Daily dosage is orally

up to 50, pref. upto 10mg/kg, and parenterally up to 5, pref. upto 1mg/kg. (I) may be administered combined with e.g. a beta-adrenergic block, a calcium channel blocker, an **ACE inhibitor** or a diuretidis
Dwg.0/0
Dwg.0/0

L18 ANSWER 22 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1992-359018 [44] WPIDS
DNC C1992-159387
TI New polar-substd. thiophene- or furan-derivs. of heterocyclyl methyl benzene - are **angiotensin II antagonists** used for treating hypertension, congestive heart failure, migraine, **Alzheimer**'s disease, anxiety, schizophrenia etc..
DC B02 B03
IN ALLEN, E E; GLINKA, T W; KEVIN, N; RIVERO, R A
PA (MERI) MERCK & CO INC
CYC 11
PI EP 510812 A1 19921028 (199244)* EN 155p
R: CH DE FR GB IT LI NL
CA 2063856 A 19921027 (199303)
JP 05194500 A 19930803 (199335) 110p
US 5252574 A 19931012 (199342) 71p
JP 07017636 B2 19950301 (199513) 130p
ADT EP 510812 A1 EP 1992-302494 19920324; CA 2063856 A CA 1992-2063856 19920324; JP 05194500 A JP 1992-117905 19920326; US 5252574 A CIP of US 1991-691911 19910426, US 1992-846152 19920311; JP 07017636 B2 JP 1992-117905 19920326
FDT JP 07017636 B2 Based on JP 05194500
PRAI US 1991-691911 19910426; US 1992-846152 19920311
AB EP 510812 A UPAB: 19931116
Furan or thiophene derivs. of formula (I) and their salts are new. Q = Q1-Q3. One of X1-X4 = O, S, SO or SO2, another is CZ (where Z is CN or a deriv. of CO2H, SO3H, NHSO2, PO3H2, triazolyl or tetrazolyl) and the other two are opt. substd. CH, dotted line represents one single and one double bond, J1 and K1 = CM or together with L = (opt. substd.) fused benzene ring or K1-L = fused pyridine ring, M = O, S, NH or NAr, Ar = opt. substd. aryl, R1 = up to 6C alkyl, alkenyl or alkynyl (all opt. substd. with halo, Ar, OH (opt. substd.) amino etc.) or (opt. substd.) (hetero)aryl, E = bond, SOn(CH2)s or O, n = 0-2, s = 0-5, one of J2 and K2 = CM and the other is CR17, R16 = 2-10C alkenyl, 2-10C alkynyl, 1-10C opt. substd. alkyl or opt. substd. aryl, R17, R18 = H, SH, CHO, (hetero)aryl, halo, OH, alkoxy, ((di)alkly)amino, COOR2, SO3R2 etc., R2 = H, alkyl, aryl or CH2 aryl, R9, R10 = H, halo, NO2, up to 6C alkyl, acyloxy, cycloalkyl or alkoxy, NHSO2R, SO2NHR, CF3, furyl, aryl etc., or R9 and R10 together form an aryl ring.
USE - (I) and (a) **angiotensin II antagonists** useful for treating hypertension and congestive heart failure, (b) CNS-active agents useful for treating cognitive dysfunctions, e.g. **Alzheimer**'s disease, amnesia and **senile dementia**, (c) anxiolytics and antidepressants and (d) antidopaminergic agents e.g. for treating schizophrenia. They may also be used to treat hyperaldosteronism, renal failure and vascular disorders such as Raynaud's disease and migraine.
0/0
Dwg.0/0

L18 ANSWER 23 OF 23 WPIDS (C) 2003 THOMSON DERWENT
AN 1992-317996 [39] WPIDS
DNC C1992-141236

TI New imidazo (1,2-b)(1,2,4)triazole(s) are **angiotensin II antagonists** - for treating hypertension, anxiety, depression congestive heart failure, migraine etc..
DC B02
IN ASHTON, W T; HUTCHINS, S M; MACCOSS, M
PA (MERI) MERCK & CO INC
CYC 10
PI EP 505111 A2 19920923 (199239)* EN 48p
R: CH DE FR GB IT LI NL
CA 2063494 A 19920923 (199250)
US 5187179 A 19930216 (199309) 27p
JP 05097854 A 19930420 (199320) 41p
EP 505111 A3 19920930 (199340)
JP 07088385 B2 19950927 (199543) 41p
ADT EP 505111 A2 EP 1992-302181 19920313; CA 2063494 A CA 1992-2063494 19920319; US 5187179 A US 1991-673630 19910322; JP 05097854 A JP 1992-65350 19920323; EP 505111 A3 EP 1992-302181 19920313; JP 07088385 B2 JP 1992-65350 19920323
FDT JP 07088385 B2 Based on JP 05097854
PRAI US 1991-673630 19910322
AB EP 505111 A UPAB: 19931129
Imidazo(1,2-b)(1,2,4) triazole derivs. of formula (I) and their salts are new: R1 = COOR5, SO3R5, NHSO2CF3, PO(OR5)2, SO2NHR9, CONHOR5, SO2NH-Het, CH2SO2NH-Het, etc.; Het = 5- or 6-membered heteroaryl ring contg. 1-3 of O, N and/or S and opt. mono- or di-substd. by OH, SH, 1-4C alkyl, 14C alkoxy, CF3, Cl, Br, F, I, NO2, COOH, 2-5C alkoxycarbonyl, NH2 or mono- or di-(1-4C)alkylamino; Het1 = heteroaryl; R2a,R2b = H, Cl, Br, I, F, NO2, NH2, 1-4C alkylamino, SSO2NHR9, CF3, 1-4C alkyl, or 1-4C alkoxy; or R2a+R2b, on adjacent C, can form a phenyl ring; R3a = H, Cl, Br, F, 1-6C alkyl, 1-6C alkoxy-(1-4C)alkyl; R3b = H, Cl, Br, I, F, NO2, 1-6C alkyl, 2-6C alkylcarbonyloxy, SO2NHR9, furyl, etc.; or R3a+R3b, on adjacent C can form a phenyl ring; R3 = H or CH(R4)OCOR4a; R4 = H, 1-6C alkyl, aryl or arylmethyl; R4a = 1-6C alkyl, aryl or arylmethyl; R6 = aryl opt. mono- or di-substd. by Cl, Br, I, F, 1-4C alkoxy, 1-4C alkyl, NO2, CF3, SO2NR9R10, etc.; R7, R8 = H, 1-10C alkyl opt. substd. by 1 or more of I, Br, Cl, F, OH, 1-10C alkoxy, 2-6C alkoxycarbonyl, 2-5C alkylcarbonyloxy, 3-8C cycloalkyl, etc.; R9 = H, 1-5C alkyl, aryl, or arylmethyl; R10 = H, or 1-4C alkyl; or R9R10 = (CH2)m; E = single bond, -NR13(CH2)s-, -S(O)x(CH2)s- (x = 0-2, s = 0-5), -CH(OH), O(CH2)s or -CO-; m = 3-6; R13 = H, 1-4C acyl, 1-6C allyl, allyl, 3-6C cycloalkyl, Ph or benzyl; X = bond, CO, O, S, OCH2, CH2O, SCH2, CH2S, NHC(R9)(R10), N(R9)SO2, SO2NR9, C(R9)(R0)NH, CH=CH, CF=CF, CH=CF, etc. u = 1-2.

USE - (I) are **angiotensin II antagonists** useful for treating hypertension, acute and chronic congestive heart failure, secondary pulmonary hyperaldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and secondary pulmonary hypertension, renal failure (e.g diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, end stage renal disease and renal transplant therapy), renal vascular hypertension, left ventriculur dysfunction, diabetic retinopathy and vascular disorders (e.g. migraine, Raynaud's disease and luminal hyperplasia) and minimising the atherosclerotic process. Dose is 1-1000 (pref. 2.5-250, esp. 2.5-75) mg/day. (I) can also be used to treat elevated intraocular pressure. (I) can also be administered in combination with other antihypertensives and/or diuretics and/or **angiotensin** in **converting enzyme inhibitors** and/or calcium channel blockers. (I) also have CNS activity and can be used to treat cognitive dysfunctions (e.g. **Alzheimers** disease, amnesia and **senile dementia**), and as anxiolytics, antidepressant and antidopaminergics (antipsychotics). Dose is 5-6000

(pref. 10-4000, esp. 20-2000) mg/day.
0/0
Dwg.0/0

L20 ANSWER 1 OF 1 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-594404 [56] WPIDS
CR 1999-312396 [26]
DNC C2000-177565
TI Inhibiting first-pass effects of orally administered materials by **co-administering** with first-pass inhibitors, provides reliable and safe first pass effect inhibition using citrus-based compositions.
DC B02 D13
IN HARRIS, J W
PA (BIOA-N) BIOAVAILABILITY SYSTEMS LLC
CYC 89
PI WO 2000054768 A1 20000921 (200056)* EN 193p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000039977 A 20001004 (200101)
ZA 2001007553 A 20020424 (200237) 192p
ADT WO 2000054768 A1 WO 2000-US2517 20000217; AU 2000039977 A AU 2000-39977 20000217; ZA 2001007553 A ZA 2001-7553 20010913
FDT AU 2000039977 A Based on WO 200054768
PRAI US 1999-251467 19990217
AB WO 200054768 A UPAB: 20020613
NOVELTY - Novel method of inhibiting the first-pass effect of orally administered materials that are subject to a first-pass effect comprises **co-administering** to the patient the material and a second compound selected from spiro-fused heterocycles (I) or (II).

DETAILED DESCRIPTION - Novel method of inhibiting the first-pass effect of orally administered materials that are subject to a first-pass effect comprises **co-administering** to the patient the material and a second compound selected from spiro-fused heterocycles of formula (I) or (II).

INDEPENDENT CLAIMS are also included for:

(1) improved methods of designing inhibitors of enzymes or polypeptides, by modification of (I) or (II); and

(2) method for preparing grapefruit juice-derived solids preparations, comprising:

(a) passing grapefruit juice through an initial filter with a filter size at least 200 micro m to produce an initial filtrate; and passing the initial filtrate through a filter with a filter size of 25 - 75 micro m, thereby trapping the grapefruit-derived solids on the filter; or

(b) centrifuging the grapefruit juice at 1000 G for 10 minutes to produce a supernatant and a pellet, optionally resuspending the pellet in water and re-centrifuging to produce a washed pellet of grapefruit-derived solids.

USE - The methods are used to **inhibit** the first-pass effect of orally administered materials that are subject to a first-pass effect (claimed) such as drugs consisting of charged, uncharged, hydrophilic, zwitterionic and/or hydrophobic species including analgesics, antibiotics, antirheumatics, anti-asthmatics, muscle relaxants, narcotic

antagonists, non-steroidal anti-inflammatory drugs, anesthetics, anti-inflammatories, neuromuscular blockers, sedatives, antimicrobials, anti-arthritics, anticancer agents, aminoglycosides, antifungals, antimalarials, antiparasitics, antituberculars, anti-arrhythmics, antivirals, carbapenems, cephalosporins, fluoroquinolones, macrolides, penicillins, sulfonamides, tetracyclines, cardiovascular agents, cholinergic agonists, **angiotensin II antagonists**, **angiotensin-converting enzyme inhibitors**, protease **inhibitors**, renin **inhibitors**, anti-adrenergic agents, antidysrhythmics, antihyperlipidiemics, antihypotensives, antihypertensives, antiplatelet agents, beta blockers, calcium channel blockers, diuretics, nitrates, pressors, steroids, thrombolytics, contrast media, dermatology agents, antibacterials, endocrine and metabolic agents, androgens/anabolic steroids, bisphosphonates, corticosteroids, chemotherapeutics, anti-diabetics, gout-related agents, minerals, nutritionals, thyroid agents, vitamins, antihistamines, antitussives, decongestants, gastroenterology agents, anti-diarrheals, anti-emetics, anti-ulcer agents, hematology agents, anticoagulants, immunosuppressants, neurological agents, anticonvulsants, antimigraine agents, parkinsonism agents, obstetric and gynecology agents, estrogens, gonadotropin-releasing hormone agonists, appetite suppressants, hormone replacement combinations, labor-induction agents, hormonal agents, progestins, tocolytics, oncology agents, ophthalmology agents, corticosteroids, glaucoma agents, psychiatric agents, **Alzheimer**'s disease agents, antidepressants, tranquilizers, antispasmodics, contraceptives, antimaniacs, antipsychotics, anxiolytics/hypnotics, drug-dependence therapy agents, sympathomimetics, stimulants, anorexiants, receptor agonists, receptor **antagonists**, pulmonary agents, urology agents, bladder spasm agents, erectile dysfunction agents, opioids, nephrolithiasis agents, prostate cancer agents and vasoconstrictors e.g. saquinavir, indinavir, L-deprenyl, tacrolimus, Sandimmune (RTM: cyclosporin A), Neoral, (RTM: cyclosporin A), nelfinavir, VX-478/141 W94, felodipine, nifedipine or sumatriptan as well as ABT-378, acebutolol, acyclovir, aldesleukin, alfentanil, alteplace, amikacin, amphotericin B, amprenavir, anistreplase, atacurium, auranofin, azithromycin, azthreonam, **benazepril**, bisulfan, bleomycin, bretylium, bromocriptine, budesonide, buspirone, capreomycin, carbenicillin, carboplatin, carmustine, carvedilol, cefaclor, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, cephalothin, cephapirin, chlorpromazine, cisplatin, clemastine, cyclosporin, cytarabine, desipramine, didanosine, dobutamine, doxepin, doxorubicin, edrophonium, erythromycin, esmolol, ethosuximide, felodipine, fentanyl, flumazenil, fluorouracil, foscarnet, **fosinopril**, ganciclovir, gentamicin, heparin, hydralazine, imipramine, indinavir, isradipine, kanamycin, ketamine, labetolol, L-deprenyl, lidocaine, lincomycin, **lisinopril**, lovastatin, nelfinavir, mercaptopurine, methicillin, methohexital, metocurine, metoprolol, mezlocillin, morphine, moxalactam, nabumetone, nadolol, nafcillin, nalbuphine, naloxone, naltrexone, netilmicin, nicardipine, nicotine, nimodipine, nitrendipine, nitroglycerin, norfloxacin, octreotide, oxacillin, paclitaxel, pancuronium, pentamidine, pentoxifylline, pipercuronium, piperacillin, pravastatin, propranolol, pyridostigmine, rifabutin, rimantandine, saquinavir, scopolamine, selegiline, sertraline, simvastatin, spironolactone, streptokinase, streptomycin, sufentanil, sumatriptan, tacrine, tacrolimus, tamoxifen, teniposide, terbutaline, terfenadine, thiopental, ticarcillin, tipranavir, tobramycin, triamcinolone acetonide, tubocurarine, vancomycin, vecuronium, venlafaxine and verapamil.

ADVANTAGE - The methods provide reliable and safe compositions that are citrus-based and contain no, or reduced, amounts of low molecular

weight phototoxic furocoumarins. They provide consistent first pass-inhibiting activity. They use first-pass inhibitors (bioenhancers and inhibitors) in non-natural and non-commercially occurring forms.
Dwg.0/2

L21 ANSWER 1 OF 4 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-403147 [38] WPIDS
CR 2003-403146 [38]
DNC C2003-107362
TI Use of **angiotensin converting enzyme inhibitor** for reducing diabetes or for slowing or reversing the decline of beta-cell function.
DC B02
IN **YUSUF, S**
PA (KING-N) KING PHARM RES & DEV INC
CYC 101
PI WO 2003032965 A2 20030424 (200338)* EN 11p
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2003032965 A2 WO 2002-US33213 20021017
PRAI US 2001-344495P 20011017
AB WO2003032965 A UPAB: 20030616
NOVELTY - Use of **angiotensin converting enzyme inhibitor** for reducing diabetes or for slowing or reversing the decline of beta-cell function is new.

DETAILED DESCRIPTION - (A) Reducing diabetes in a patient at risk of developing diabetes involves administering **angiotensin converting enzyme** (**ACE**) **inhibitor** for sufficient period of time to prevent the development of diabetes.

An INDEPENDENT CLAIM is also included for (B) slowing or reversing the decline of beta cell function in an individual involving administering an **ACE inhibitor.**

ACTIVITY - Antidiabetic.

5720 Patients having evidence of vascular disease or who had diabetes and one other risk factor were administered either **ramipril** (10 mg) (test) or placebo once per day. Follow-up visits occurred at 1 month and 6 months after randomization and then every 6 months. At each visit it was documented whether diagnosis of diabetes was made since last visit. It was observed that only 102 (i.e. 3.6%) patients treated with test reported new diagnosis of diabetes as compared to 155 (i.e. 5.4%) placebo treated patients. The proportion of patients in test group was significantly lower compared to that in placebo.

MECHANISM OF ACTION - **ACE inhibitor.**

USE - For reducing diabetes (especially type 2 diabetes) in patients at risk for developing diabetes.
Dwg.0/2
TECH UPTX: 20030616
TECHNOLOGY FOCUS - PHARMACEUTICALS - In (A): the diabetes is type 2 diabetes. The beta cell function in such an individual is slowed or reversed. The method increases the islet blood flow, increases beta-cell perfusion, reduces insulin resistance in skeletal muscles, increases insulin mediated glucose disposal, and increases insulin-mediated glucose

uptake by skeletal muscles.

L21 ANSWER 2 OF 4 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-403146 [38] WPIDS
CR 2003-403147 [38]
DNC C2003-107361
TI Use of **angiotensin converting enzyme inhibitor** especially **ramipril** for e.g. preventing or reducing onset of diabetes and for reversing decline of beta-cell function.
DC B02
IN **YUSUF, S**
PA (AVET) AVENTIS PHARMA DEUT GMBH
CYC 101
PI WO 2003032963 A2 20030424 (200338)* EN 9p
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2003032963 A2 WO 2002-EP11636 20021017
PRAI US 2001-344495P 20011017
AB WO2003032963 A UPAB: 20030616
NOVELTY - Use of **angiotensin converting enzyme** (**ACE**) **inhibitor** for: (A) reducing diabetes in patients at risk of developing diabetes; (B) slowing or reversing the decline of beta cell function; (C) for increasing islet blood flow; (D) increasing pancreatic beta cell perfusion; and (E) lowering aldosterone secretion and renal potassium wasting, is new.

DETAILED DESCRIPTION - (A) Reducing diabetes in patients who are at risk for developing diabetes comprises administering an **angiotensin converting enzyme** (**ACE**) **inhibitor** for sufficient period of time to prevent the development of diabetes.

INDEPENDENT CLAIMS are also included for methods of: (B) slowing or reversing the decline of beta cell function; (C) increasing islet blood flow; (D) increasing pancreatic beta cell perfusion; and (E) lowering aldosterone secretion and renal potassium wasting, comprising administering an ACE.

ACTIVITY - Antidiabetic.

5720 Patients having evidence of vascular disease or who had diabetes and one other risk factor were administered either **ramipril** (10 mg) (test) or placebo once per day. Follow-up visits occurred at 1 month and 6 months after randomization and then every 6 months. At each visit it was documented whether diagnosis of diabetes was made since last visit. It was observed that only 102 (i.e. 3.6%) patients treated with test reported new diagnosis of diabetes as compared to 155 (i.e. 5.4%) placebo treated patients. The proportion of patients in test treated group was significantly lower compared to placebo.

MECHANISM OF ACTION - **ACE inhibitor**.

USE - For reducing diabetes in patients at risk for developing diabetes, especially type 2 diabetes (claimed).

Dwg.0/0

L21 ANSWER 3 OF 4 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-290268 [30] WPIDS
DNC C2001-088856
TI Use of a renin-angiotensin system inhibitor or derivative in the and

manufacture of a medicament and prevention of stroke in patients exhibiting normal or low blood pressure, diabetes and congestive heart failure.

DC B05

IN BENDER, N; DAGENAIS, G; GERSTEIN, H; LJUNGGREN, A; RANGOONWALA, B; SCHOELKENS, B; **YUSUF, S**; DAGANAIS, G

PA (AVET) AVENTIS PHARMA DEUT GMBH

CYC 94

PI WO 2001015673 A2 20010308 (200130)* EN 17p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
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AU 2000076484 A 20010326 (200137)
BR 2000013540 A 20020430 (200237)
NO 2002000850 A 20020221 (200238)
EP 1212081 A2 20020612 (200239) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2002000644 A3 20020515 (200241)
SK 2002000270 A3 20020910 (200274)
KR 2002060167 A 20020716 (200305)
HU 2002002461 A2 20021228 (200308)
JP 2003508426 W 20030304 (200319) 32p
CN 1384756 A 20021211 (200324)
ZA 2002001471 A 20030528 (200341) 48p

ADT WO 2001015673 A2 WO 2000-EP8341 20000825; AU 2000076484 A AU 2000-76484 20000825; BR 2000013540 A BR 2000-13540 20000825, WO 2000-EP8341 20000825; NO 2002000850 A WO 2000-EP8341 20000825, NO 2002-850 20020221; EP 1212081 A2 EP 2000-965898 20000825, WO 2000-EP8341 20000825; CZ 2002000644 A3 WO 2000-EP8341 20000825, CZ 2002-644 20000825; SK 2002000270 A3 WO 2000-EP8341 20000825, SK 2002-270 20000825; KR 2002060167 A KR 2002-702521 20020226; HU 2002002461 A2 WO 2000-EP8341 20000825, HU 2002-2461 20000825; JP 2003508426 W WO 2000-EP8341 20000825, JP 2001-519887 20000825; CN 1384756 A CN 2000-811070 20000825; ZA 2002001471 A ZA 2002-1471 20020221

FDT AU 2000076484 A Based on WO 200115673; BR 2000013540 A Based on WO 200115673; EP 1212081 A2 Based on WO 200115673; CZ 2002000644 A3 Based on WO 200115673; SK 2002000270 A3 Based on WO 200115673; HU 2002002461 A2 Based on WO 200115673; JP 2003508426 W Based on WO 200115673

PRAI SE 1999-3028 19990827

AB WO 200115673 A UPAB: 20010603
NOVELTY - Novel use of an inhibitor of the renin-angiotensin system or derivative (I) in the manufacture of a medicament for the prevention of stroke in patients exhibiting normal or low blood pressure, diabetes and/ or congestive heart failure (CHF) with no pre-existing CHF.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: a method of preventing of stroke in patients exhibiting normal or low blood pressure, diabetes and/ or congestive heart failure (CHF) with no pre-existing CHF; and a formulation for use in the prevention of stroke in patients exhibiting normal or low blood pressure, diabetes and/ or congestive heart failure (CHF) with no pre-existing CHF.

ACTIVITY - Cerebroprotective; Cardiant; Antidiabetic.

Treating 9,541 patients who are at risk for cardiovascular events due to a history of previous ischemic heart disease, stroke, peripheral arterial disease or individuals with diabetes with **ramipril** for 6 years resulted in a 32% reduction in the number of patients who developed a stroke, 21% who developed congestive heart failure, and 36% reduction who developed diabetes.

MECHANISM OF ACTION - **Angiotensin converting enzyme (ACE) inhibitor**; an angiotensin II antagonist

USE - (I) is used in the prevention of stroke in patients exhibiting normal or low blood pressure, diabetes and/ or congestive heart failure (CHF) with no pre-existing CHF.

Dwg.0/0

TECH UPTX: 20010603

TECHNOLOGY FOCUS - PHARMACEUTICALS - The **inhibitor** of the renin-angiotensin system is an **angiotensin converting enzyme (ACE) inhibitor**, an angiotensin II antagonist or their derivatives.

The **ACE inhibitor** is selected from alacepril, alatriopril, altiopril calcium, ancovenin, **benazepril**, benzazepril hydrochloride, benzazeprilat, benzoylcaptopril, **captopril**, **captopril**-cysteine, **captopril** -glutathione, ceranapril, ceranopril, **ceronapril**, cilazapril, cilazaprilat, delapril, delapril-diacid, **enalapril**, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosfenopril sodium, **fosinopril**, **fosinopril** sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, **imidapril**, indolapril, indolaprilat, libenzapril, **lisinopril**, lyciumin A, lyciumin B, mixanpril, **moexipril**, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, **perindopril**, perindoprilat, pivalopril, pivopril, **quinapril**, **quinapril** hydrochloride, quinaprilat, **ramipril**, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, **trandolapril**, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril or zofenoprilat especially **ramipril**, ramiprilat, **lisinopril**, **enalapril** or enalaprilat.

The angiotensin II antagonist is candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan or eprosartan especially candesartan and candesartan cilexetil.

L21 ANSWER 4 OF 4 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-265856 [27] WPIDS
DNC C2001-080427
TI Use of an inhibitor of the renin-angiotensin system optionally with an other antihypertensive, or cholesterol lowering agent, or diuretic or aspirin in the manufacture of a medicament for the prevention of myocardial infarction or stroke.
DC B05 C03
IN BENDER, N; DAGANAIS, G; GERSTEIN, H; RANGOONWALA, B; SCHOELKENS, B; **YUSUF, S**
PA (AVET) AVENTIS PHARMA DEUT GMBH
CYC 94
PI WO 2001015674 A2 20010308 (200127)* EN 33p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000076491 A 20010326 (200137)
BR 2000013704 A 20020507 (200238)
NO 2002000978 A 20020418 (200239)
EP 1216038 A2 20020626 (200249) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

CZ 2002000770 A3 20020612 (200251)
SK 2002000269 A3 20020702 (200253)
KR 2002040795 A 20020530 (200276)
CN 1368881 A 20020911 (200282)
HU 2002003326 A2 20030228 (200330)

ADT WO 2001015674 A2 WO 2000-EP8461 20000830; AU 2000076491 A AU 2000-76491 20000830; BR 2000013704 A BR 2000-13704 20000830, WO 2000-EP8461 20000830; NO 2002000978 A WO 2000-EP8461 20000830, NO 2002-978 20020227; EP 1216038 A2 EP 2000-965906 20000830, WO 2000-EP8461 20000830; CZ 2002000770 A3 WO 2000-EP8461 20000830, CZ 2002-770 20000830; SK 2002000269 A3 WO 2000-EP8461 20000830, SK 2002-269 20000830; KR 2002040795 A KR 2002-702626 20020227; CN 1368881 A CN 2000-811394 20000830; HU 2002003326 A2 WO 2000-EP8461 20000830, HU 2002-3326 20000830

FDT AU 2000076491 A Based on WO 200115674; BR 2000013704 A Based on WO 200115674; EP 1216038 A2 Based on WO 200115674; CZ 2002000770 A3 Based on WO 200115674; SK 2002000269 A3 Based on WO 200115674; HU 2002003326 A2 Based on WO 200115674

PRAI US 1999-151436P 19990830

AB WO 200115674 A UPAB: 20010518

NOVELTY - Use of an inhibitor of the renin-angiotensin system or derivative (I) optionally with an other antihypertensive, or a cholesterol lowering agent, or a diuretic or aspirin in the manufacture of a medicament for the prevention of cardiovascular events is new.

DETAILED DESCRIPTION - Use of an inhibitor of the renin-angiotensin system or derivative, optionally with an other antihypertensive, or a cholesterol lowering agent, or a diuretic or aspirin in the manufacture of a medicament for the prevention of cardiovascular events is new.

INDEPENDENT CLAIMS are also included for:

(1) a combination product containing (I) and a cholesterol lowering agent;

(2) a method of preventing cardiovascular events comprising administering (I) optionally with an other antihypertensive, or a cholesterol lowering agent, or a diuretic or aspirin

ACTIVITY - Cerebroprotective; Cardiant; Antianginal; Antidiabetic; Nephrotropic.

Treating 1000 patients with **ramipril** for 4 years prevented 160 patients from experiencing strokes, cardiac arrests, new heart failure, diabetic complications, revascularization rates or myocardial infarction.

MECHANISM OF ACTION - Renin-angiotensin inhibitor; calcium channel blocker; beta blocker.

USE - (I) is used to treat a patient with an increased cardiovascular risk due to a manifest coronary heart disease, a history of transient ischemic attacks or strokes, or a history of peripheral vascular disease. (I) is also used in the manufacture of a medicament for the prevention of myocardial infarction, stroke, congestive heart failure (in a patient not previously having congestive heart failure), worsening angina, cardiac arrest, revascularization procedures, cardiovascular death, diabetes, diabetic complications or overt nephropathy in a diabetic patient.

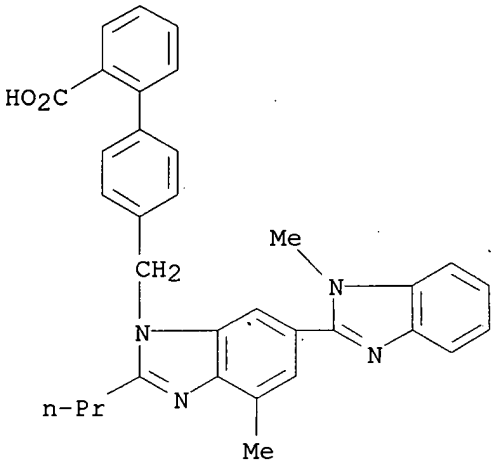
Dwg.0/0

TECH UPTX: 20010518

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred **Inhibitor**: The **inhibitor** of the renin-angiotensin system is an **angiotensin converting enzyme inhibitor**, an angiotensin II antagonist or their derivatives. The **angiotensin converting enzyme inhibitor** is omapatrilat, MDL100240, alacepril, **benazepril**, **captopril**, cilazapril, delapril, **enalapril**, enalaprilat, **fosinopril**, fosinoprilat, **imidapril**, **lisinopril**, **perindopril**, **quinapril**,

ramipril, ramiprilat, saralasin acetate, temocapril, **trandolapril**, trandolaprilat, ceranapril, **moexipril**, quinaprilat, spirapril or their derivatives.
The angiotensin II antagonist is saralasin acetate. candesartan cilexetil, valsartan, candesartan, losartan potassium, eprosartan, irbesartan, tasosartan, telmisartan or their derivatives.
The cholesterol lowering agent is a statin, preferably lovastatin, pravastatin, simvastatin or fluvastatin.
The antihypertensive is a calcium channel blocker or a beta blocker.

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 144701-48-4 REGISTRY
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4'-[[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl]-2-biphenylcarboxylic acid
CN BIBR 277
CN BIBR 277SE
CN Micardis
CN Pritor
CN **Telmisartan**
FS 3D CONCORD
MF C33 H30 N4 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

170 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
172 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  IMIDAPRIL/CN
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=> d l16 1-19

L16  ANSWER 1 OF 19  REGISTRY  COPYRIGHT 2003 ACS
RN   217460-19-0  REGISTRY
CN   1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-
     (ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, monohydrochloride,
     (2S,3aS,7aS)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Perindopril hydrochloride
FS   STEREOSEARCH
MF   C19 H32 N2 O5 . Cl H
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
CRN  (82834-16-0)

Absolute stereochemistry.
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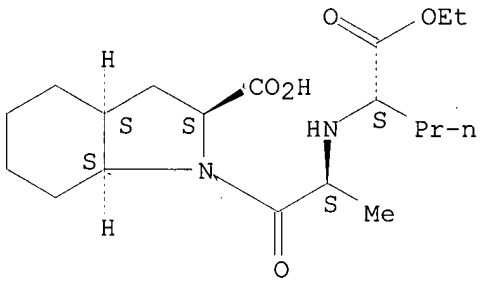


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HCl

  1 REFERENCES IN FILE CA (1957 TO DATE)
  1 REFERENCES IN FILE CAPLUS (1957 TO DATE)
```
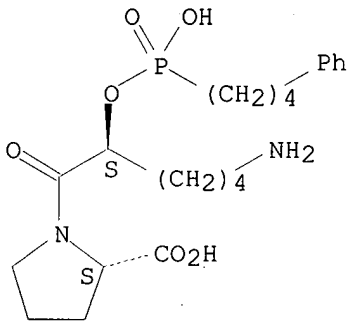

=>

L16 ANSWER 2 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 111223-26-8 REGISTRY
CN L-Proline, 1-[(2S)-6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 1-[6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-, (S)-
OTHER NAMES:
CN Ceranapril
CN **Ceronapril**
CN SQ 29852
FS STEREOSEARCH
DR 124760-68-5, 120122-26-1
MF C21 H33 N2 O6 P
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



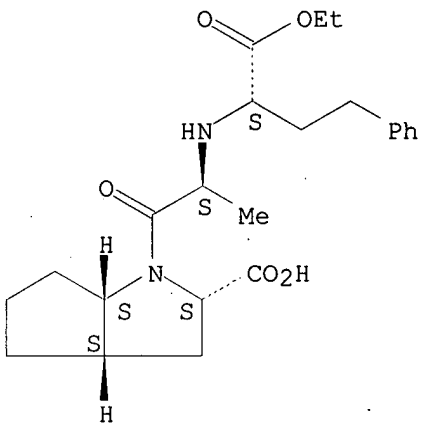
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

138 REFERENCES IN FILE CA (1957 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
138 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 3 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 104196-00-1 REGISTRY
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, (2S,3aS,6aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, [2S-[1[R*(R*)],2.alpha.,3a.beta.,6a.beta.]]-
OTHER NAMES:
CN **Ramipril hydrochloride**
FS STEREOSEARCH

MF C23 H32 N2 O5 . Cl H
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, DRUGPAT, DRUGUPDATES, USPATFULL
CRN (87333-19-5)

Absolute stereochemistry.

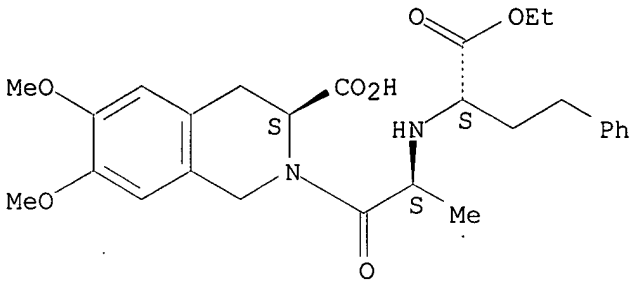


● HCl

4 REFERENCES IN FILE CA (1957 TO DATE)
4 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 4 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 103775-10-6 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, (3S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN **Moexipril**
CN RS 10085
FS STEREOSEARCH
DR 109715-88-0
MF C27 H34 N2 O7
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.

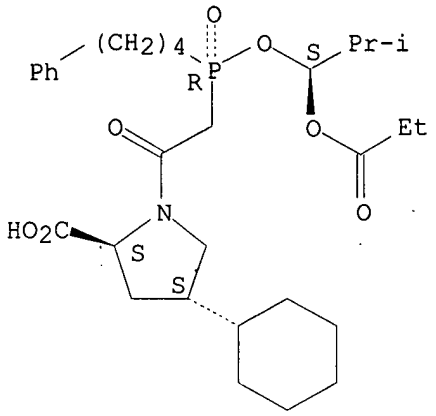


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

90 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
90 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 5 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 98048-97-6 REGISTRY
CN L-Proline, 4-cyclohexyl-1-[[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, [1[S*(R*)],2.alpha.,4.beta.]-
OTHER NAMES:
CN Fosenopril
CN **Fosinopril**
FS STEREOSEARCH
DR 128947-97-7, 97825-24-6
MF C30 H46 N O7 P
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



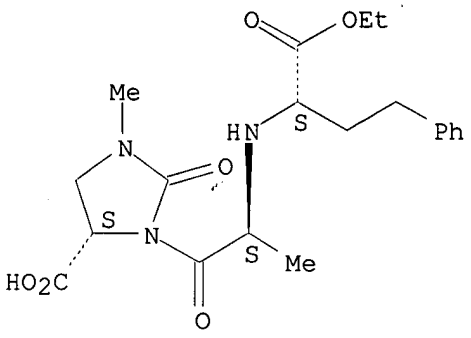
5

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

359 REFERENCES IN FILE CA (1957 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
360 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 6 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 89396-94-1 REGISTRY
CN 4-Imidazolidinecarboxylic acid, 3-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, monohydrochloride, (4S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4-Imidazolidinecarboxylic acid, 3-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, monohydrochloride, [4S-[3[R*(R*)],4R*]]-
OTHER NAMES:
CN **Imidapril hydrochloride**
CN Novaloc
CN TA 6366
CN Tanapril
FS STEREOSEARCH
MF C20 H27 N3 O6 . Cl H
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMINFORMRX, CIN, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
CRN (89371-37-9)

Absolute stereochemistry.



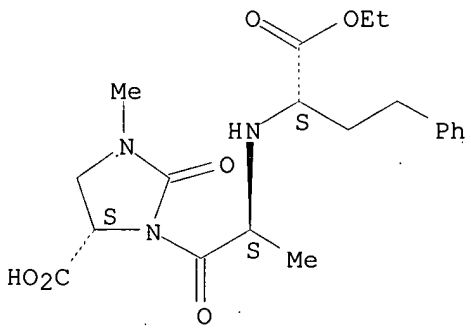
6

● HCl

21 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
21 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 7 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 89371-37-9 REGISTRY
CN 4-Imidazolidinecarboxylic acid, 3-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4-Imidazolidinecarboxylic acid, 3-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-, [4S-[3[R*(R*)],4R*]]-
OTHER NAMES:
CN **Imidapril**
FS STEREOSEARCH
MF C20 H27 N3 O6
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



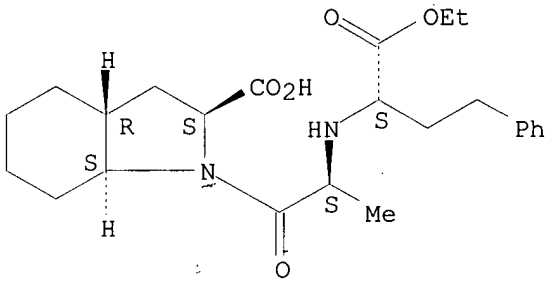
7

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

187 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
188 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 8 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 87725-72-2 REGISTRY
CN 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, (2S,3aR,7aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, monohydrochloride, [2S-[1[R*(R*)],2.alpha.,3a.alpha.,7a.beta.]]-
OTHER NAMES:
CN **Trandolapril hydrochloride**
FS STEREOSEARCH
MF C24 H34 N2 O5 . Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS, DRUGPAT, DRUGUPDATES, USPATFULL
(*File contains numerically searchable property data)
CRN (87679-37-6)

Absolute stereochemistry. Rotation (-).



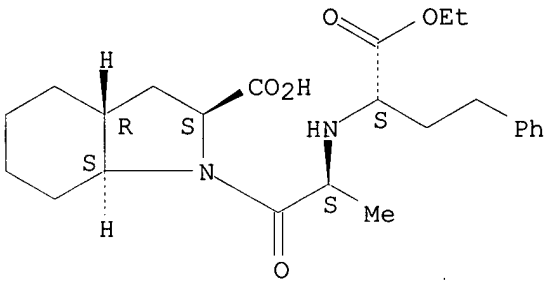
● HCl

5 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 9 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 87679-37-6 REGISTRY
CN 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aR,7aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2.alpha.,3a.alpha.,7a.beta.]]-
OTHER NAMES:
CN Gopten
CN Odrik

CN RU 44570
CN **Trandolapril**
FS STEREOSEARCH
MF C24 H34 N2 O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry. Rotation (-).



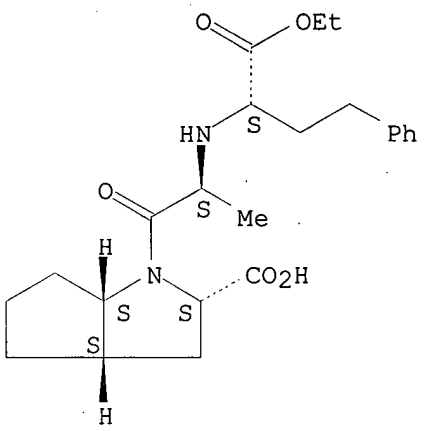
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

324 REFERENCES IN FILE CA (1957 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
325 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 10 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 87333-19-5 REGISTRY
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,6aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2.alpha.,3a.beta.,6a.beta.]]-
OTHER NAMES:
CN Altace
CN Cardace
CN Delix
CN HOE 498
CN Pramace
CN Quark
CN Ramace
CN **Ramipril**
CN Triatec
CN Tritace
CN Unipril
CN Vesdil
FS STEREOSEARCH
DR 126613-39-6
MF C23 H32 N2 O5

CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



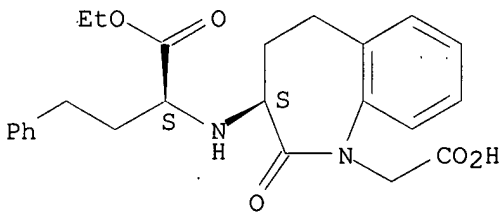
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

715 REFERENCES IN FILE CA (1957 TO DATE)
15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
720 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 11 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 86541-75-5 REGISTRY
CN 1H-1-Benzazepine-1-acetic acid, 3-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, [S-(R*,R*)]-
OTHER NAMES:
CN Benapril
CN **Benazepril**
CN Briem
CN Cibacen
CN Cibacen WS
CN Cibacene
FS STEREOSEARCH
DR 116764-54-6
MF C24 H28 N2 O5
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.

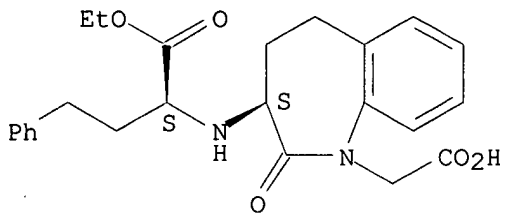


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

326 REFERENCES IN FILE CA (1957 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
330 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 12 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 86541-74-4 REGISTRY
CN 1H-1-Benzazepine-1-acetic acid, 3-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, (3S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, [S-(R*,R*)]-
OTHER NAMES:
CN **Benazepril hydrochloride**
CN CGS 14824A
CN CGS 14824A HCl
CN Lotensin
CN Lotension
FS STEREOSEARCH
DR 211307-81-2
MF C24 H28 N2 O5 . Cl H
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CIN, CSCHEM, DIOGENES, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
CRN (86541-75-5)

Absolute stereochemistry.



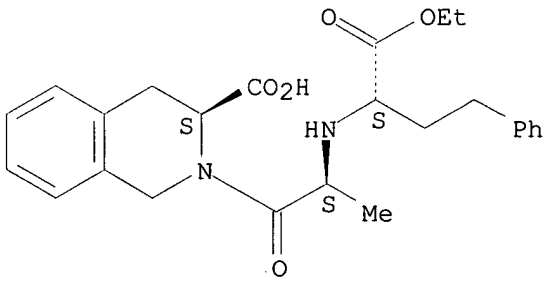
● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

54 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
54 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 13 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 85441-61-8 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN Ectren
CN Koretic
CN **Quinapril**
FS STEREOSEARCH
MF C25 H30 N2 O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.

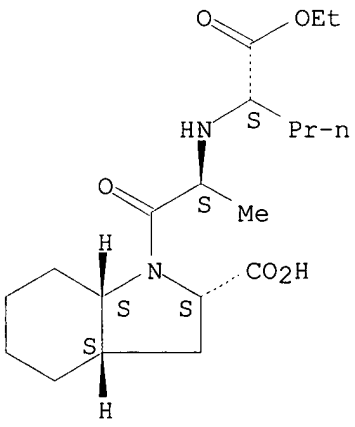


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

444 REFERENCES IN FILE CA (1957 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
445 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 14 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 82834-16-0 REGISTRY
CN 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,7aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2.alpha.,3a.beta.,7a.beta.]]-
OTHER NAMES:
CN McN-A 2833
CN **Perindopril**
CN S 9490
FS STEREOSEARCH
DR 99149-83-4
MF C19 H32 N2 O5
CI COM
LC STN Files: ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



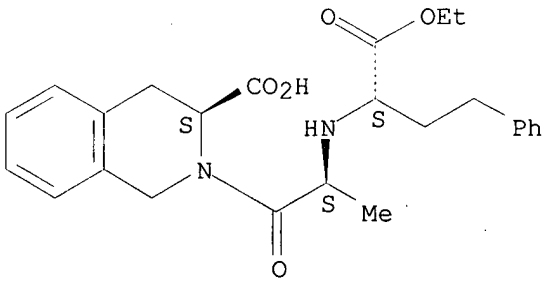
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

553 REFERENCES IN FILE CA (1957 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
554 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 15 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 82586-55-8 REGISTRY

CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN Accupril
CN Accuprin
CN Accupro
CN Accupron
CN Acequide
CN Acequin
CN Acuitel
CN Acuprel
CN Acupril
CN Asig
CN CI 906
CN Korec
CN Korectic
CN PD 109452-2
CN **Quinapril hydrochloride**
CN Quinazil
FS STEREOSEARCH
MF C25 H30 N2 O5 . Cl H
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (85441-61-8)

Absolute stereochemistry.



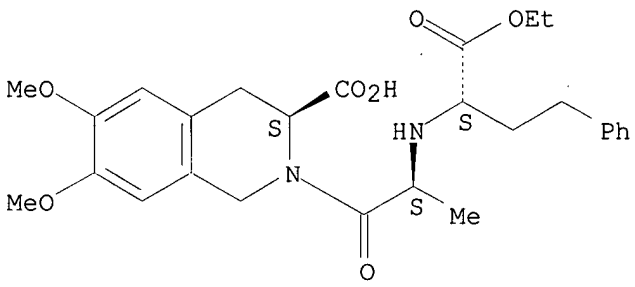
● HCl

55 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
55 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 16 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 82586-52-5 REGISTRY
CN 3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-

phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, [3S-[2[R*(R*)],3R*]]-
OTHER NAMES:
CN CI 925
CN **Moexipril hydrochloride**
CN RS 10085-197
CN SPM 925
CN Univasc
FS STEREOSEARCH
MF C27 H34 N2 O7 . Cl H
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CIN, DIOGENES, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
CRN (103775-10-6)

Absolute stereochemistry.



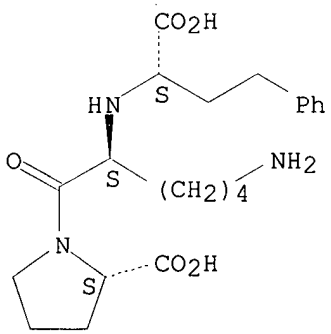
● HCl

18 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
18 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 17 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 76547-98-3 REGISTRY
CN L-Proline, N2-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-, (S)-
OTHER NAMES:
CN Acerbon
CN Alapril
CN Carace
CN Cipral
CN Cipril
CN Coric
CN Inopril
CN Linopril
CN Linvas

CN Lipril
CN **Lisinopril**
CN Lisipril
CN Lisoril
CN Lispril
CN Listril
CN MK 521
CN MK 522
CN N-(1(S)-Carboxy-3-phenylpropyl)-L-lysyl-L-proline
CN N2-[(S)-1-Carboxy-3-phenylpropyl]-L-lysyl-L-proline
CN Noperten
CN Novatec
CN Presiten
CN Prinil
CN Prinivil
CN Prinvil
CN Tensopril
CN Tensyn
CN Vivatec
CN Zestril
FS STEREOSEARCH
MF C21 H31 N3 O5
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIUDB, IPA, MEDLINE, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



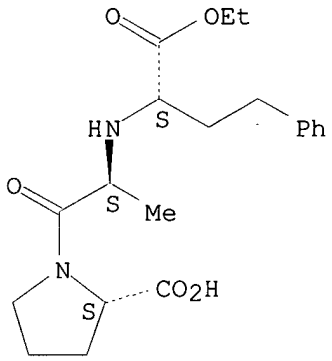
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

979 REFERENCES IN FILE CA (1957 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
989 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 18 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 75847-73-3 REGISTRY
CN L-Proline, N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN L-Proline, 1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-
OTHER NAMES:
CN **Enalapril**
FS STEREOSEARCH
DR 172964-46-4, 77549-58-7
MF C20 H28 N2 O5
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry. Rotation (-).



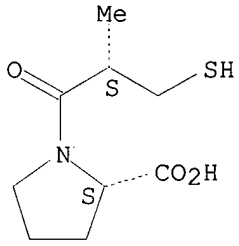
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2015 REFERENCES IN FILE CA (1957 TO DATE)
25 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2020 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 19 OF 19 REGISTRY COPYRIGHT 2003 ACS
RN 62571-86-2 REGISTRY
CN L-Proline, 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Proline, 1-(3-mercapto-2-methyl-1-oxopropyl)-, (S)-
OTHER NAMES:
CN (-)-Captopril
CN Acediur
CN Aceplus
CN Acepress
CN Acepril
CN Alopresin
CN Capoten
CN Captolane
CN **Captopril**
CN Captoril
CN Cesplon
CN Dilabar

CN Garranil
CN Hipertil
CN L-Captopril
CN Lopirin
CN Lopril
CN Novocaptopril
CN S-Captopril
CN SA 333
CN SQ 14225
CN Tensiomin
CN Tensobon
CN Tensoprel
FS STEREOSEARCH
DR 138452-88-7, 70903-77-4, 225661-74-5
MF C9 H15 N O3 S
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4186 REFERENCES IN FILE CA (1957 TO DATE)
75 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4193 REFERENCES IN FILE CAPLUS (1957 TO DATE)